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THE AMNIOTIC FLUID

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'Premature rupture of the membranes causes delay in the first stage of labour'. True or false? Most doctors, when asked this question would answer without hesitation: 'True'. When challenged, they would quote with some indignation (and every justification) such eminent authorities as Comyns Berkeley, Victor Bonney, Whitridge Williams,[1] Munro Kerr,[2] and Dugald Baird,[3] who, for half a century, have taught that 'the bag of forewaters acts as a fluid wedge which dilates the cervix during labour', and 'the absence of this wedge, as in early rupture of the membranes, causes delay in the first stage'.

Any doctor who practises obstetrics knows that if there is delay in the first stage, and he wishes to accelerate delivery, he ruptures the membranes thereby destroying the very wedge which is said to be so valuable. No further argument is needed to show that the importance of this dilating wedge is a myth. The myth owes its origin, no doubt, to the fact that premature rupture of the membranes is often associated with some abnormality such as disproportion or malpresentation which, in itself, gives rise to delay.

Medicine has suffered too much from myths of this sort, which, once born, are nourished by constant repetition until they acquire the status of fact. Another example of this process comes immediately to mind. 'Oligohydramnios does not give rise to any maternal symptoms'.[4] This statement is widely accepted as being correct. In fact, it would be true to say that variations in the volume of the amniotic fluid are generally regarded as being of no consequence unless there is gross polyhydramnios.

DECREASED LIQUOR AMNII

A decrease in the volume of liquor amnii at the end of pregnancy is probably a normal phenomenon. Indeed, it has been suggested that the consequent reduction in the size of the uterus is the factor which initiates labour[5] and that insensitivity to this change is one of the causes of postmaturity. In these cases, the liquor continues to be absorbed and, by the time the patient finally goes into labour, has become greatly diminished in amount (oligohydramnios) or is completely absent (anhydramnios). The first case of anhydramnios described[5] occurred in Cape Town and is worth recording again, since it illustrates clearly the syndrome which is typical of the condition.

Case Report

Mrs. N.K., aged 24, had been well throughout pregnancy (her first). There appeared to be no obstetric abnormality whatsoever. Labour began spontaneously 14 days after her estimated date of confinement. The contractions were mild at first and the patient did not enter the nursing home until 12 hours after their onset. The foetus was in the LOA position, with the head fixed and the heart sounds audible. The cervix was one-fifth dilated. During the next 6 hours labour seemed normal though not strong, and the head descended slowly. However, 4 hours later (22 hours after the onset of labour) the contractions became strong and irregular, the intervals between them varying from 1 to 7 minutes. The foetal heart rate was normal. The cervix was two-fifths dilated and well applied to the presenting part. It was noted at this time that there was no bag of forewaters, though the membranes had not ruptured. Pethidine, 100 mg., was administered and repeated after 3 hours.

Twenty-seven hours after the onset of labour the attendants were distressed to find that the foetal heart sounds could no longer be heard. The contractions were still irregular and vaginal examination showed little further progress. The patient's general condition, however, was good. She was given ¼ gr. of morphine and was then able to sleep between contractions. Four hours later it became necessary to repeat the morphine in order to control the contractions which had again become very strong.

When labour had been in progress for 35 hours and had been well established for 18 hours, vaginal examination showed that no further progress had been made. The patient's general condition was still good, her morale was excellent, and it was still hoped that vaginal delivery would be possible. Delivery by Caesarean section was naturally viewed with the greatest reluctance since the foetus was dead.

However, after another 4 hours uterine action had again become tonic and incoordinate, the lower segment was ballooning and there was a marked Bandl's ring. There was no further cervical dilatation. Rupture of the uterus was now imminent. It was decided that, notwithstanding the absence of foetal heart sounds, Caesarean section was necessary in the interests of the mother.

When, at operation, a distended thin-walled lower segment was incised, a small amount of glutinous green material was all that escaped. The foetus, weighing 6 lb., was delivered easily. The thick upper segment, which was sharply demarcated from the lower segment and about half its size, contained no fluid whatsoever. The membranes had not ruptured during labour and at no time had any leaking of liquor been detected.

The cardinal features of this case are: (1) Postmaturity, (2) anhydramnios, (3) incoordinate uterine action, and (4) intrauterine death of the foetus.

Comment

Since anhydramnios was first described in 1954 it has been the practice in Cape Town maternity hospitals to observe and record any deficiency in the volume of liquor amnii, and there is now no doubt that anhydramnios, or marked oligohydramnios, is dangerous both to baby and mother. In a case of postmaturity the possibility of anhydram-

nios should always be borne in mind. Frequently cases of postmaturity are induced surgically, and the opportunity exists for gauging the volume of liquor. The observation is made more accurately and more easily with the aid of the Drew-Smythe catheter which taps the amniotic sac above the foetal head. If anhydramnios is diagnosed, the patient must be watched with the greatest care, for from the moment that labour begins, the baby's life will be in danger. In the absence of liquor amnii, the foetus is not cushioned from the direct pressure of the contracting uterine walls. Moreover, the uterus itself is liable at any time to go into spasm. From the onset of labour, therefore, the foetal heart should be auscultated at half-hourly intervals, while oxytocics should be withheld for fear of precipitating incoordinate uterine action. If labour proceeds smoothly and is expected to be short, no interference is necessary as a rule. However, the foetal heart is liable to stop without warning, and if the baby is to be saved facilities for immediate Caesarean section must be available throughout labour.

There appears to be an individual predisposition to anhydramnios. Mrs. N.K. has since been delivered of 2 live babies by Caesarean section. At the first operation (at term) the uterus contained only 2 oz. of liquor. The baby had a right talipes equinovarus. The second operation was performed at 38 weeks; the amount of liquor was normal and there was no foetal abnormality.

POLYHYDRAMNIOS

An excess of liquor amnii is commonly referred to as hydramnios. This is inaccurate, for the word hydramnios is merely a literal translation into Greek of the Latin words liquor amnii. An abnormal deficiency of amniotic fluid is universally known as oligohydramnios. Its natural and logical antithesis is polyhydramnios. The aetiology of polyhydramnios is obscure. Its importance lies in its frequent association with certain morbid conditions of the mother and foetus. These conditions fall into 3 groups:

1. Uniovular twin pregnancy, where the polyhydramnios affects only the sac of the larger twin.
2. Foetal deformities, such as anencephalus (but not hydrocephalus), spina bifida, and talipes.
3. Less frequently, maternal diseases such as diabetes, pre-eclamptic toxaemia, and cardiac or renal disease causing oedema of the placenta.

Polyhydramnios is usually a chronic condition which does not become clinically recognizable until the 4th or 5th month of pregnancy. As a rule no treatment is called for, although during labour the possibility of malpresentation and prolapse of the cord must be kept in mind. Occasionally the onset is acute and the symptoms caused by the sudden distension of the uterus are correspondingly severe. In the acute condition it is necessary to remove sufficient liquor to relieve the embarrassment of cardiac and respiratory action. This is best done by means of the Drew-Smythe intra-amniotic catheter so that the rate of withdrawal is well controlled. The operation may have to be repeated from time to time.

Diagnosis is usually easy, though occasionally polyhydramnios may be confused with an ovarian cyst. It is helpful to remember that the cervix is pulled upwards by a distended uterus, while a large ovarian cyst pushes it downwards. X-rays and the presence or absence of a uterine souffle will also help. Where an ovarian cyst co-exists with pregnancy the diagnosis may be more difficult. A distended bladder associated with an incarcerated retroverted gravid uterus sometimes causes difficulty in diagnosis, but is soon recognized when the catheter is used.

ABORTION

There is reason to believe that abortion is sometimes caused by failure of the mechanism which controls the volume of the amniotic fluid.[6] If the liquid is absorbed or ceases to be secreted in normal amounts, the uterus, deprived of its cushioning effect, becomes irritable and expels the embryo. Unfortunately this knowledge is of little practical value, since no means is known of maintaining or restoring the normal fluid volume.

A variant of this condition is, however, amenable to treatment. It sometimes happens that the internal os lacks the tone necessary to support the uterine contents. The amniotic sac then bulges through the os and eventually ruptures. Liquor amnii escapes, the uterus becomes irritable and the foetus is expelled. This condition, first described by Shirodkar,[7] is commonly known as 'the incompetent os'. There is usually a history suggesting trauma to the sphincter, such as previous precipitate labour. Subsequent pregnancies run a normal course until the 4th month, but at any time between then and the 7th month liquor amnii begins to escape. Examination will reveal a toneless patulous cervix, with membranes (if they have not already ruptured) bulging through the os. Occasionally, if the patient is put to bed at once and remains there, it is possible to prolong pregnancy until the child is viable. Usually, however, liquor continues to escape and before long the uterus expels the foetus. Subsequent pregnancies will follow a similar course unless the condition is cured. Fortunately operative treatment gives good results. Operative treatment is usually undertaken shortly before the 4th month of pregnancy. The bladder is stripped off the anterior surface of the cervix as in colporrhaphy. A purse-string suture is now passed round the cervix deep to the mucosa in the region of the internal os. The material used varies with individual preference. Fascia lata, heavily stranded chromic catgut, and nylon sutures have all been used. The use of nylon sutures is probably the most satisfactory, though this method has the disadvantage that the sutures must be removed to allow delivery per vagina. Delivery by Caesarean section is considered by some to be the method of choice in these cases.

The Shirodkar operation gives excellent results when performed for the condition for which it was designed. Unfortunately there are already signs that it is becoming 'fashionable', and perhaps it is as well to mention that it will cure no other type of habitual abortion.

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EDITORIAL : VAN DIE REDAKSIE

ENDOCRINE THERAPY IN ENDOMETRIOSIS

In the past the use of hormones in gynaecology has met with success, but perhaps more often with failure. This result can, no doubt, be partly ascribed to abuse—it is unfortunately not always remembered that no benefit can be expected from the indiscriminate use of hormones. However, failure should not discourage, but rather stimulate thought and research in this field, and a careful search should be made for the particular gynaecological conditions for which endocrine therapy is indicated. One of the problems that calls for a full investigation is the scope of endocrine treatment in endometriosis. In recent years there has been an increasing interest in the potentialities of endocrine therapy in endometriosis. This is a hopeful step in the approach to a disease for which present-day treatment is far from satisfactory.

There is no doubt that endometriosis is a common clinical disorder. In most cases treatment has been surgical and often, of necessity, radical, entailing the removal of both ovaries. This approach is all too frequently undesirable because the majority of cases occur between the ages of 30-40 years and younger. Conservative surgical treatment may be successful, but the success is often of a temporary nature. Moreover, surgical treatment may not be feasible.

Since the disease cannot exist in the absence of the ovarian hormones, endocrine therapy appeared to be a rational form of treatment and, in 1948, the use of large doses of stilboestrol was suggested. This was not followed by extensive use of oestrogens, because of certain drawbacks associated with therapy of this nature. Another approach arose as a result of the observation that existing endometriosis may be improved by pregnancy. The amelioration of endometriosis during pregnancy is thought to be due to the formation of decidua and subsequent necrosis in the areas of endometriosis.[1] With the discovery of the newer and more potent progesterones, a few cases have been treated with these substances by inducing a state of 'pseudo pregnancy'. It is too early to assess the results of this therapy, and the rationale is open to some doubt on pathological grounds. Moreover, the cost of the hormones required for this type of treatment is at present very high.

Androgen therapy has been abused in gynaecology and is frowned upon. Nevertheless, with increasing experience during the past twenty-five years, the reluctance to use androgens is giving way to the knowledge that in androgen therapy the therapeutic dose can be small and safe. Yet it still remains important to be on the look-out for undesirable effects. Androgens have been used on a small scale in the treatment of endometriosis, but detailed and long-term results have not been reported to any extent. In an article in this issue of the *Journal* the largest series of cases of endometriosis treated with androgens, with a detailed follow-up study of up to nine years, is reported. Although 25 per cent of the patients were completely resistant to treatment, the fact that 75 per cent responded (36 per cent temporarily and 38 percent permanently) is a finding of great importance.

With the dosage employed adverse side-effects were negligible. It appears that androgens can safely be used, firstly, in carrying out a therapeutic test when the diagnosis is in doubt and, secondly, in the many cases where conservative surgery had failed or where radical surgery is undesirable. The routine use of androgens pre- and especially postoperatively would appear to deserve careful consideration. However, as pointed out in the article, only half the cases seen in clinical practice are suitable for a trial with this therapy.

While surgery will probably remain the chief method of treatment for some time to come, endocrine therapy might have an important place in selected cases. The results of further clinical trials with androgens and progesterone will be awaited with interest. It is gratifying that the subject of endocrine treatment in endometriosis will be discussed at the forthcoming South African Medical Congress in East London. This will emphasize the importance of finding additional methods of dealing with a common clinical problem, the treatment of which has, up to the present time, left much to be desired.

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SORGBEHOEWENDE KINDERS

By 'n vorige geleentheid[1] het ons aangetoon dat hierdie eeu met sy besondere spanninge en druktes vir die geneesheer van die moderne tyd probleme geskep het wat sy voorgangers in die beroep nie geken het nie. Ons het toe ook aangetoon dat die verskynsel van die ontwortelde mens waarmee elke dokter vandag in die uitoefening van sy praktyk te doen kry, een van die groot probleme van ons tyd is.

Een van die spesiale vorms wat die verskynsel van die ontwortelde mens in ons land aanneem, is die probleem van die sorgbehoewende kind. Onder die term sorgbehoewende kind sluit ons in alle kinders wat nie noodwendig aan die een of ander liggaamlike of geestessiekte ly nie, maar wat verwaarloos is in so 'n mate dat die samelewing moet ingryp by hul versorging. Wat die presiese omvang van hierdie

probleem is, is nie maklik om te bepaal nie. Wat ons egter wel weet is dat daar in ons land 'n stelsel van tehuise en industrieskole bestaan waartoe sorgbehoewende kinders in duisendtalle toegelaat word.

Wat in hierdie verband veral ontstellend is, is nie soseer die bestaan van die probleem van die sorgbehoewende kind as sodanig nie—dié probleem sal altyd daar wees. Maar, dit is die spesifieke vorm wat die probleem in ons land aanneem wat verontrustend is.

Betroubare navorsing het byvoorbeeld onlangs aan die lig gebring—hierdie feite is ontleen aan 'n proefskrif wat dr. I. J. J. van Rooyen vir die graad D.Phil aan die Universiteit van Suid-Afrika voorgelê het — dat slegs 13 persent van die 2,001 blanke sorgbehoewende kinders wat hy ondersoek het, weens die dood of siekte van hul ouers na kindertehuise gestuur is. Die meeste kinders van hierdie groep, ongeveer 70 persent, het in tehuise beland omdat hulle deur hul ouers verwaarloos is. Wat die aantal dogters in die ondersoek betref wat aan onsedelikheid skuldig was, kom nie minder nie as 64 persent uit redelike goeie huise.

Hierby moet ook nog dr. van Rooyen se bevinding gevoeg word dat een van die grootste alleenstaande faktore wat sorgbehoewendheid by kinders in die hand werk, drankmisbruik deur die ouers is, veral deur die vaders. Daar is ook ander nadelige invloede wat tot 'n mindere of meerdere mate onder die gesinne in die ondersoek voorgekom het, byvoorbeeld armoede, swak huislike toestande oor die algemeen, 'n swak omgewing, onsedelikheid onder die ouers, rusie of onenigheid in die huis, en die werkende moeder wat haar kinders verwaarloos.

Hierdie feite is onstellend omdat hulle 'n refleksie is van die gebrekkige integriteit en solidariteit van die huisgesin in ons land. As dokters, wie se werk dit uit die aard van die saak meebring dat ons gedurig met ons pasiënte op 'n besondere intieme en persoonlike vlak verkeer, kan ons ons nie van hierdie probleemgesteldheid losmaak nie. Ons weet maar te goed dat gebrekkige huise lei tot gebroke persone—tot ongelukkigheid en wanaanpassing en ontreddering, en uiteindelik tot liggaamlike- en geestessiekte.

As 'n mediese beroep moet ons dus ons kragte saamsnoer met almal wat in hierdie saak wil optree. Dr. Van Rooyen bepleit veral drie metodes wat gevolg moet word met die doel om hierdie leemte uit die weg te probeer ruim: (1) Dat meer en doeltreffender pogings aangewend moet word om ouers te rehabiliteer—hierdie benadering tot die probleem word alreeds met groot welslae deur verskeie welsynsorganisasies gevolg; (2) dat die hele probleem van die verkryging van geskikte pleegouers ondersoek word—voorstelle tot verandering van die Kinderwet is alreeds in die Parlement bespreek; en (3) dat 'n groter mate van huislike atmosfeer in die kindertehuise geskep moet word.

Wat ook al die oplossing van hierdie vraagstuk mag wees, wil dit vir ons voorkom of die tyd ryp is vir 'n deurtastende ondersoek van staatsweë, sowel as deur gemeenskaps- en welsynsorganisasies, na die vraagstuk van die sorgbehoewende kind, in die besonder, en na metodes en maniere waarop die morele en maatskaplike fondamente van ons gesinstruktuur in die algemeen verstewig kan word.

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TAALRUBRIEK

Die Taalkomitee van die Geneeskundige Skool van die Universiteit Stellenbosch stel voor om te gebruik:

1. Eng. tone: Afr. *tonus* (teenoor Eng. tension: Afr. *spanning*).

2. Eng. incidence: Afr. *insidensie*. Volgens die verband kan 'n mens dikwels volstaan met te sê iets kom baie of min voor, soms pas *voorkoms* ook, en as 'n mens presieser gegewens het, kan *voorkomssyfer* ook nuttig wees. Maar *insidensie* pas oral, daarom word dit voorgestel.

3. Eng. nurse. Die algemene Afrikaans is *verpleegster*, deesdae al hoe meer met 'n vorm *verpleër* daarnaas vir die manlike. Dit werk goed. Maar hoe nou gemaak met die aanspreekvorm? ‚Verpleegster, bring asb. vir my . . . ' klink 'n bietjie vol in die mond. Tog weet die komitee geen beter raad nie en beveel hy dus aan: verpleegster, ook as aanspreekvorm. Daarnaas sou ons dan die rangonderskeidings *stafverpleegster* en *suster* hê.

4. Eng. forceps. Eng. artery-forceps: Afr. *klem*.
Eng. pincette: Afr. *pinset*.
Eng. forceps: Afr. *tang*.

5. Eng. schizophrenia: Afr. *skisofrenie*.

6. Eng. trachea: Afr. *tragea*, mv. *trageas*.

7. Eng. bronchus: Afr. *brongus*, mv. *brongusse* en *brongi*. Wie Latyn wil skrywe, bly natuurlik vry om dit te doen: bronchus, bronchi.

8. Eng. pendulous: Afr. *hang-* met samestellinge, dus bv. pendulous tumour: hangtumor, pendulous abdomen: hangbuik, net soos bv. hangore, hangskouers, e.d.m.

9. Eng. rigid (ity; i.v.m. spiere): Afr. *styf*, *styfheid* met graadvariante soos *stywigheid*, en besondere benoeminge soos *hard* (bv. by peritonitis).

10. Eng. application (of foetal head or of cervix to foetal head): Afr. *pas*, as s.nw. èn as ww.

11. Eng. predispose: Afr. *predisponeer*.

12. Eng. lumbar puncture: Afr. *lumbale punksie*. *Lumbaalpunksie* sou ook verdedigbaar gewees het indien ons 'n s.nw. lumbaal gehad het. Maar ons het dit nie: ons *lumbaal* is 'n b.nw. En dié soort b.nw. word gewoonlik verbuig: dus *lumbale*, en dan net soos die meeste ander b.nwe. los geskrywe van die volgende s.nw., soos hierbo.

13. Eng. virulent: Afr. *virulent*. Ons kan daarop let dat die aksent in Afr. op die lènt val, dus virulènt, net soos assistènt, presidènt, e.s.m.

14. Eng. artefact: Afr. *artefak*, nie artefak*t* nie: ons skrywe of sê selde of nooit in Afrikaans 'n *t* of 'n *d* aan die end van 'n woord na f, g, k, p of s nie. Daarom is ook al voorgestel *sis* (en nie sist nie).

15. Eng. eminence: Afr. *verhewenheid*.

16. Eng. protuberance: Afr. *uitsteeksel*.

THE SCOPE OF ENDOCRINE TREATMENT IN ENDOMETRIOSIS

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Has endocrine therapy any place in the treatment of endometriosis? The answer to this question is a matter of considerable clinical importance because present-day therapy of this condition is not satisfactory. The elimination of ovarian function by surgery or radiation will cure the disease. This is not the solution, however, because the majority of cases occur between the ages of 30 and 40 years, and a number under the age of 30 years. Conservative surgery may be successful in younger patients, but, owing to the site and extent of the disease or its recurrence after operation, the results of treatment of this nature are in many cases unsatisfactory. Like the normal uterine endometrium, endometriosis is responsive to the ovarian hormones, and indeed cannot exist in their absence. Hormonal therapy, therefore, suggests itself as a rational form of treatment in selected cases. However, the place, if any, for such treatment has not yet been settled.

In an attempt to determine whether endocrine therapy is of value, an investigation was carried out on 120 consecutive cases of endometriosis, 60 of which were treated with hormones. This investigation was prompted by the clinical problem presented by 2 patients who were first seen in 1950:

Case 1

Mrs. R.C., aged 31, married for 3 years, nulliparous, was seen on 17 March 1950. She complained of severe dyspareunia, increasing dysmenorrhoea which necessitated her taking to bed for 2 days each month, and a continual pain in the right iliac fossa. Three years previously endometriomatous cysts were removed from both ovaries by a left salpingo-oophorectomy and a partial resection of the right ovary. Her symptoms improved for 2 months, but then recurred, more severely than before. Examination revealed an anteverted uterus, a tender right ovary, the size of a hen's egg, and tender nodules in the right uterosacral ligament which, on palpation, reproduced a pain identical to the dyspareunia. The endometriosis had obviously recurred. She pleaded for something to be done, even if the treatment had to be radical. Another operation, however, might have necessitated the removal of the rest of her right ovary, and radiotherapy would have been as drastic. Androgen therapy (the details of which are described below) was prescribed. She reported back 10 weeks later to say that she was 'a different person'. The dyspareunia, dysmenorrhoea, and pain had disappeared. The ovary was smaller, though still tender, and the nodules in the uterosacral ligament had also decreased in size. The course of androgens was repeated after a 2 months' interval. She has now been followed up for 9 years and there has been no recurrence.

Case 2

The satisfactory result achieved in Case 1 encouraged the use of a similar course of androgens in another patient with endometriosis, Mrs. H.A.R., aged 34, nulliparous, who complained of pain in the left iliac fossa and dysmenorrhoea of 4 months' duration. A tender fixed ovarian cyst, 2½ inches in diameter, was felt in the left ovary and purple nodules were seen and felt in the rectovaginal septum. Neither this course of androgens, nor a second one, had any effect on her symptoms and signs. A laparotomy was performed and a large endometriomatous cyst was resected from her left ovary and a smaller one from the right.

An exploration of the literature on endocrine therapy in endometriosis revealed a sparseness of papers and the fact that relatively few cases had been reported.[3,5-7,9,10,15,18] The need for more extensive clinical research was therefore indicated. This investigation was started in an attempt to assess the exact place of hormonal therapy in the present-day treatment of endometriosis. The 120 cases encountered represent 3% of 4,200 consecutive White gynaecological patients seen during the period. Sixty of the cases were not treated with hormones because (*a*) associated pathology was present, e.g. fibroids, (*b*) the diagnosis was not made before operation, (*c*) the pathology was endometriosis interna (uterine adenomyosis), or (*d*) the diagnosis was doubtful and it was considered unwise to postpone operation (e.g. there were big ovarian tumours which may have been neoplastic).

THE CHOICE OF HORMONE AND THE DOSAGE

The hormones that may be considered for the treatment of endometriosis are oestrogens, progesterone, or androgens.

1. *Oestrogens*

In 1948 Karnaky[7] suggested the use of very large doses of stilboestrol, and reported 25 cases with satisfactory results. He started with ½ mg. of stilboestrol daily, increasing the dose every 4th day until 5 mg. had been given. This dosage was continued until the patient began to bleed, when the amount was increased to 10 mg. every 15 minutes so that the bleeding stopped. Then 15 mg. was given nightly until the patient bled again, at which time 20 mg. was given every 15 minutes until the bleeding stopped once more. The patients were kept amenorrhoeic for 3-6 months—these colossal doses being increased each time they bled, and Karnaky found that to achieve this he had to continue increasing the dose every 2-6 weeks. Thereafter the administration of stilboestrol was gradually discontinued. He was so enthusiastic about this treatment that he predicted that it would in time become one of the most important forms of therapy for endometriosis.

Since then, however, only a few cases treated in this way have been reported,[15] although Cooke[3] described 33 cases. Most gynaecologists have been sceptical or afraid to try this form of treatment because (*a*) non-pregnant women usually become nauseous and vomit on 5 mg. of stilboestrol, let alone the very large doses recommended by Karnaky (stilboestrol was tried in 3 cases in this series but had to be abandoned after a short while because of uncontrollable vomiting), (*b*) clinical research over long periods of time would be necessary to ascertain the possible carcinogenic effects of such prolonged and massive therapy, (*c*) small doses would obviously aggravate endometriosis, and (*d*) Scott[16] found that in a group of monkeys with experimentally produced endometriosis the lesion did not disappear after large doses of oestrogens were given; in fact it became hyperplastic after about 2 years.

2. *Progesterone*

The use of progesterone in the treatment of endometriosis (with or without oestrogens) is a subject for clinical research, because some cases of endometriosis are thought to be cured by pregnancy[8,14,16] (i.e. in the relatively few cases where conception occurs). Kistner[8] recently treated 12 patients with large doses of both oestrogen and the newer, more potent, progesterones for 2-7 months. Of these patients 9 showed

subjective and objective evidence of improvement, but the author admits that no conclusions can yet be drawn regarding the long-term effect of this treatment.

The rationale of treating endometriosis with progesterone is acceptable in cases where the aberrant endometrium is responsive to both oestrogen and progesterone. More often, however, the lesion is of an immature or 'unripe' variety,[11] and in such cases the ectopic endometrium does not respond to progesterone. It is unreasonable to expect a cure in these 'unripe' varieties. Two of our cases are at present undergoing a trial treatment with progesterone, and in these cases histological examination of the ectopic endometrium in the premenstrual phase of the cycle showed a proliferative phase, while that of the normal uterine endometrium was secretory in type.

The results of further clinical trials must be awaited before the therapeutic effect of progesterone on endometriosis can be assessed.

3. *Androgens*

There is still reluctance, and even rather violent opposition, on the part of many practitioners (and patients) to the use of androgen therapy for gynaecological conditions. This attitude probably stems from the time, about 25 years ago, when the use of androgens was first introduced as a form of gynaecological treatment, and when the dosage was purely empirical. We now know, however, that very big doses were administered at that time, with the result that dramatic virilizing effects occurred. The experience of the past 25 years has clearly shown that the therapeutic dose of androgens is but a fraction of what it used to be in the early experimental days. By giving androgens in correct doses, their therapeutic properties can be utilized without the risk, or with the negligible risk of producing virilizing phenomena.[1,2,4,12] When clinicians were first feeling their way with androgen therapy, very large doses of 500 mg. of testosterone proprionate (equivalent to 2,500 mg. of methyl testosterone by mouth) were given monthly. About 20% of cases then developed virilizing phenomena (acne, hirsutism, lowering of the voice pitch, and enlargement of the clitoris). All subsequent reports, however, have shown that if 300-500 mg. of methyl testosterone are given monthly for 2 consecutive months, the risks of any virilizing effects are less than 1% and, if treatment is stopped as soon as such symptoms appear, the symptoms are reversible.[1,4,12]

In this series the dosage used was the minimal and safe dose of 10 *mg. of methyl testosterone daily by mouth for* 2 *consecutive months.* Where the course had to be repeated, an interval of at least one month, and often many months,[1] was allowed between courses. In only 2 of the 60 cases was there the slightest suggestion of virilizing phenomena. One patient complained of a transitory tenderness of the clitoris; the other, during the 5th course (she had the largest number of courses in the series) began to notice a slight decrease in the size of her breasts, minimal hirsutism around the nipples, and slight voice changes. However, all these symptoms disappeared on cessation of the treatment.

ANALYSIS OF THE CASES TREATED WITH ANDROGENS

A. *Patients who did not Respond*

The response to androgen therapy in the 60 cases treated is shown in Table. I. Fifteen cases (25%) did not respond at all, and had to undergo surgical treatment or other therapy.

TABLE I. RESPONSE TO ANDROGEN THERAPY IN 60 CASES

No response	15 cases (25%)
Temporarily relieved	22 cases (36·6%)
Apparently permanently cured	23 cases (38·4%)

B. *Patients who Benefited by Androgen Therapy*

The significant fact is that 75% of the cases showed improvement of varying degree up to complete cure, and that some even conceived. These cases may be divided into 4 groups (Table II):

TABLE II. ANALYSIS OF CASES THAT BENEFITED BY ANDROGEN THERAPY

Group	*Response*	*No. of Cases and percentage*
1	Temporarily relieved	22 (36·6%)
2	Completely cured of symptoms and signs. Did not conceive when complaining of infertility	7 (11·6%)
3	Completely cured of symptoms and signs. Did not conceive, but did not complain of infertility	7 (11·6%)
4	Completely cured of symptoms and signs and conceived. Complained of infertility	9 (15·2%)
		45 (75%)

Group 1

Twenty-two cases (36·6%) were temporarily relieved, but the condition recurred. In these cases surgical treatment was carried out, or at least advised. In this group also were some patients whose symptoms were kept under control

TABLE III. CASES TEMPORARILY RELIEVED—NO. OF MONTHS OF RELIEF

Months	1	2	3	4	5	6	12	24	36
No. of cases (22)	0	2	7	1	4	5	1	1	1

until the onset of the menopause (Table III).

Of these 2 were cured for 2 months, 7 for 3 months, 1 for 4 months, 4 for 5 months, and 5 for 6 months; 1 case was cured for a year before symptoms recurred, 1 for 2 years and 1 for 3 years. *The usual duration of temporary cure was, therefore,* 3-6 *months.*

Group 2

Seven cases (11·6%) were completely cured of all symptoms and signs but did not conceive although infertility was one of the complaints. While the results of androgen therapy were successful, the success could not be called perfect because of the failure to cure the infertility. In 6 of these cases all other investigations for infertility were negative—in 1 the husband was infertile. This persistent infertility, however, is a common experience, even when symptoms and signs are cured by surgery.

Group 3

Another group of cases, also 7 in number (11·6%), were, as far as could be ascertained, completely and apparently permanently cured, but they did not subsequently become pregnant. In no case, however, was infertility a complaint.

Group 4

Cases who can be regarded as complete cures; not only did their symptoms and signs disappear but they also became pregnant. There were 9 cases (15·2%) in this group—quite a substantial percentage in a condition which is so difficult to treat. These cases warrant more detailed analysis:

Case 1

Mrs. E.R., aged 24, had undergone a laparotomy on 30 November 1954 when a chocolate cyst the size of an orange was found in each ovary. A right salpingo-oophorectomy was performed as well as a resection of the endometriomatous part of the left ovary. Two years later she consulted me, complaining of infertility of 2 years' duration and pain in the LIF. Examination revealed an enlarged fixed tender left ovary. Phenobarbitone, ½ gr. daily for 2 months, had no effect. She was then given a course of androgen therapy. The pain and swelling of the ovary disappeared and 6 weeks after cessation of the hormonal therapy she was pregnant.

Case 2

Mrs. E.E.L., aged 26, was referred by her family doctor because of her complaint of primary infertility of 4 years' duration and increasing secondary dysmenorrhoea. A year previously he had performed an appendicectomy and had noticed endometriomatous nodules in the pelvic peritoneum, in the ovaries and in the uterosacral ligaments. Nothing was done about these lesions at the time of the operation. Examination revealed the nodules and tender adnexa. Sperm-analyses and tests for tubal patency were normal, and graphs recording basal body temperature indicated the occurrence of ovulation and also showed some pyrexia during menstruation. A month after 2 courses of androgens the patient had amenorrhoea due to pregnancy.

Case 3

Mrs. V.R.B., aged 30, complained of primary infertility of 6 years' duration as well as dysmenorrhoea and dyspareunia. All investigations were negative, except that some pyrexia at menstruation was shown on the basal temperature graph, and nodules could be felt in both uterosacral ligaments. These nodules became large and tender during menstruation. The patient was given phenobarbitone, ½ gr. daily by mouth for 2 months. There was no improvement in the dyspareunia or dysmenorrhoea. On 18 March 1957 a course of androgens was started. She reported on 12 June 1957 with amenorrhoea which was shown to be due to pregnancy.

Case 4

Mrs. S.D., aged 38, was investigated for primary infertility of 4 years' duration. Sperm-analyses were normal, her tubes were patent, and temperature recordings showed evidence of ovulation. There was also some pyrexia during menstruation and this raised the suspicion of endometriosis. During an examination under anaesthesia and a curettage to exclude endometrial tuberculosis, the left ovary was found to be enlarged and, in the immediate premenstrual phase of the cycle 2 firm nodules were felt in the left uterosacral ligament. A diagnosis of endometriosis was made and a course of androgens was commenced on 21 January 1957. Two months after this course of treatment she became pregnant.

Case 5

Mrs. L.H., aged 28, was seen on 2 July 1956 because she had been married for 7 years and was unable to conceive. On 24 June 1957 she had had an operation for endometriosis in Johannesburg. The gynaecologist who operated supplied the information that large endometriomata were resected from both ovaries. Endometriosis was also present in the uterosacral ligaments, but was not removed. The basic fertility factors were investigated and found to be normal, but both ovaries as well as both uterosacral ligaments were enlarged. Two courses of androgens were given, the second commencing on 22 October 1956. She missed her period in January 1957, and this proved to be due to a pregnancy.

Case 6

Mrs. J.V., aged 28, was referred for an opinion about her secondary infertility of 3 years' duration because her doctor had found a normal sperm count, satisfactory ovulation and tubal patency. She also complained of dyspareunia and dysmenorrhoea. On examination her left ovary was enlarged to the size of a hen's egg and tender nodules were felt in the left uterosacral ligaments. Phenobarbitone tablets, prescribed for 2 months, had no effect on the symptoms and signs. The patient was then given methyl testosterone, 10 mg. daily by mouth for 2 months. The course was commenced on 3 October 1957, and on 24 January 1958 she reported with amenorrhoea which was subsequently proved to be due to pregnancy.

Case 7

Mrs. M.F., aged 34, complained of secondary infertility for 3 years and pain in the RIF. Six months previously her doctor had operated on her for the pain and found endometriosis in the pelvic peritoneum and in both ovaries. On examination these areas were very tender. On 9 September 1953 she was given a course of androgens and 3 months later became pregnant.

Case 8

Mrs. P.F., aged 26, complained of primary infertility since her marriage 6 years previously. The left ovary was enlarged and nodules were present in the left uterosacral ligament. She also had increasing secondary dysmenorrhoea. Phenobarbitone therapy over a 2 months' period in no way improved the symptoms and signs. Three months after a course of androgen therapy, however, the ovary was no longer palpable, the nodules had disappeared, and she was pregnant.

Case 9

Mrs. B.M., aged 22, was seen on 22 March 1954. In 1951 her right ovary had been removed for a large adherent chocolate cyst and a large portion of the left ovary had also been resected. She now complained of dysmenorrhoea and dyspareunia, pain in the LIF and primary infertility for 18 months. The left ovary was enlarged to the size of a golf ball, and very tender. A course of androgens was given; the ovary decreased in size and the symptoms disappeared, but she did not conceive. She was not seen again until 19 February 1958. She said that she felt well and her symptoms had not recurred, but she was very eager to have a baby. The sperm-analysis, tubal patency and ovulation were investigated and found to be normal, but conception did not occur. She was given 2 courses of androgens with a month's interval between them. On 8 October 1958 she wrote to say that she had amenorrhoea and nausea; she was subsequently seen and found to be pregnant.

DISCUSSION

Response in Relation to the Age of Patient and Type of Lesion

In this series the response to androgen therapy did not appear to depend on the age of the patient. Young patients in the early 20's responded as well or as badly as patients over the age of 40 years. (Of those who responded 16 were 20-30, 18 were 30-40, and 11 were over 40 years of age. Of those who did not respond 5 were under 30, 8 between 30 and 40, and 2 over 40 years of age.)

The site and the extent of the lesion, however, affected the chances of success. The success rate was good when the ovaries were involved with smaller lesions or when the uterosacral ligaments or the pelvic peritoneum was affected. The diagnosis in nearly all of these latter cases was made during a previous operation (as discussed in the following paragraph). On the other hand, in 3 cases endometriosis was present in laparotomy scars and these cases did not show any improvement. In 4 cases the endometriosis was in the rectovaginal septum and these cases were also resistant to endocrine therapy. Eight of the patients had chocolate cysts bigger than 3 inches in diameter and only one of these responded.

How the Diagnosis was Made

It is well known that the diagnosis of endometriosis is sometimes very difficult. Care was taken to be sure that the patient was in fact suffering from endometriosis before considering her a suitable case for the series. This is one of the reasons why half the cases seen were excluded from the investigation. Of those treated with androgens the diagnosis was made during a previous or subsequent operation in 45 cases. In 11 of the remaining 15 the condition was felt or seen in the uterosacral ligaments or rectovaginal septum, and typical symptoms were present. In 4 of the cases the diagnosis was not proved; however, the history was typical

and enlargement of one or both ovaries was felt, and the cases responded to androgens. Clinically, therefore, there was no doubt that endometriosis was present.

The possible effect of psychotherapy on symptoms, and the possible occurrence of spontaneous cure, was considered. In 25 of the patients who responded to androgens, courses of phenobarbitone tables were given before androgens were administered. In none of these was there any improvement in symptoms and signs during the administration of the placebo (phenobarbitone).

Mode of Action of Androgens in Endometriosis

In this investigation a clinical approach to the problem of endometriosis was made and clinical facts were analysed. How 38·4% of cases are cured and 36·6% temporarily relieved by androgen therapy, is a matter for speculation. The dose used was very small. It has been shown by Salmon[12] that a dose of 300 mg. of methyl testosterone daily by mouth for a month has no effect on menstruation, pituitary gonadotrophic excretion, pregnandiol excretion, ovarian histology, endometrial histology, vaginal cytology, and basal temperature pattern. This work has been confirmed by Geist and Salmon[4], and Shorr *et al.*[17] It has, however, also been shown that a small dose of androgens is therapeutically effective in other disorders (e.g. the dysfunctional uterine haemorrhages) by directly opposing the action of the ovarian hormones.

Since the dose used in these cases did not have any effect on the *normal* intra-uterine endometrium, the ectopic endometrium of endometriosis must be much more vulnerable. This is not unreasonable, for such endometrium is in an area where it has no right to be—in the wrong 'soil' and environment.

Indications for Androgen Therapy

This investigation was carried out to determine whether androgen therapy has a place in the treatment of endometriosis. A retrospective analysis of this series shows that the treatment has a small but definite place in selected cases, and the dosage recommended is harmless. Androgen therapy is of value:

1. As a therapeutic test when the diagnosis is in doubt; *75% of patients with endometriosis who are given androgen therapy show a temporary or permanent improvement in symptoms and signs.*

2. When the condition has recurred after one or more conservative operations and the patient is too young to consider radical surgery or a radiation menopause; *a third of such cases are likely to show permanent, and a further third temporary, improvement.*

3. When the lesion is not easily accessible to surgery, e.g. diffuse spread, or its presence in the uterosacral ligaments.

4. When the patient's only complaint is infertility and the lesion is not gross.

5. In certain selected cases, who have had one or more previous operations, to tide the patient over until the menopause sets in when spontaneous cure occurs.

6. In view of the findings in this investigation it would appear that a course of androgens given *as a routine* after conservative operation for endometriosis may help to prevent recurrence in several cases. A course could also be given pre-operatively, not only because this may result in permanent cure, but also because in a substantial percentage of cases there will be a temporary improvement confirming the diagnosis and possibly rendering surgery less difficult.

SUMMARY AND CONCLUSIONS

1. In an attempt to determine the place of endocrine therapy in the treatment of endometriosis, 120 consecutive cases were analysed, 60 of whom were treated with hormones. This constitutes the largest series of cases described who were treated in this way.

2. Oestrogens, progesterone or androgens can be used. Androgen therapy is considered the most suitable form of treatment today, although progesterone therapy should be investigated more fully.

3. Androgens were used in 60 cases in courses of 10 mg. of methyl testosterone daily by mouth for 2 months. This was found to be a harmless dose. Minimal temporary side-effects occurred in 2 cases, but these phenomena disappeared on cessation of therapy.

4. Of the 60 cases 25% were completely resistant to treatment; 36·6% were temporarily cured of symptoms and signs (for 3-6 months, but occasionally for 1-3 years); 38·4% were completely and apparently permanently cured—and of this group over a third became pregnant, infertility having been one of the major complaints. The patients who became pregnant are described in detail.

5. Response to treatment does not appear to depend on the age of the patient. The site and extent of the lesion, however, did affect the chances of success. Endometriomatous cysts smaller than 3 inches in diameter in the ovaries, and lesions in the pelvic peritoneum and uterosacral ligaments responded well to androgen therapy. On the other hand, endometriosis in the rectovaginal septum and in laparotomy scars, and lesions in the ovary bigger than 3 inches in diameter, are more resistant to treatment.

6. The mode of action of endocrine therapy is discussed.

7. A retrospective analysis of this series shows that androgen therapy can be most helpful and has a small but definite place in selected cases. The dosage recommended is harmless.

This kind of treatment is indicated:

(*a*) As a therapeutic test when the diagnosis is in doubt.

(*b*) When the condition has recurred after one or more conservative operations.

(*c*) When the lesion is not easily accessible to surgery.

(*d*) When the patient's only complaint is infertility.

(*e*) In view of the findings in this investigation it would appear that the routine use of androgens to prevent the recurrence of endometriosis after conservative surgery deserves consideration; likewise a course may be of value pre-operatively.

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A CLINICAL TRIAL OF PEMPIDINE IN THE TREATMENT OF HYPERTENSION*

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Ganglion-blocking agents are undoubtedly the most potent hypotensive drugs at present available, and extensive research is being directed to the discovery of similar compounds which would be safe if given orally and would have less side-effects. At the moment, however, it is difficult to imagine that any drug whose main action is blockage of all impulses at autonomic ganglia can fail to produce unwanted parasympathetic effects. Pempidine is the most recently introduced of these compounds, and so far only one account of its use in hypertension has been published, by Harrington, Kincaid-Smith and Milne,[1] who suggested that pempidine might hold certain advantages over mecamylamine in the treatment of hypertension. Mecamylamine, a secondary amine, has been more extensively used lately than the quaternary amine derivatives such as hexamethonium, pentolinium and chlorisondamine, mainly because mecamylamine, in being rapidly and completely absorbed from the gut,[2] made oral therapy more effective and predictable. However, mecamylamine also has certain disadvantages. Since its excretion is slow and irregular,[2] toxic effects from overdosage may be prolonged for days—even with danger to life.

Paralytic ileus is the most important and serious of these side-effects. Resultant vomiting and diarrhoea may cause a reduction of renal blood-flow with further delay in excretion of the drug, and prolongation of the toxic effects. Patients with mecamylamine ileus have, on occasion, been diagnosed by unsuspecting surgeons as cases of acute intestinal obstruction, and exposed to the danger of unnecessary laparotomy.[3]

In view of these disadvantages, a safer and more effective ganglion-blocking agent has been searched for. We were consequently glad to be able to study the new drug pempidine.† Experimental studies on animals[4] have shown that pempidine acts on the autonomic ganglia and that the drug was more active and less toxic than mecamylamine.

Chemistry and Pharmacology of Pempidine

Pempidine is a tertiary amine and a simple derivative of piperidine. Pempidine is 1 : 2 : 2 : 6 pentamethylpiperidine, and is available for oral use as the bitartrate salt; but the hydrochloride is preferred for intravenous use. The drug was originally designated M. & B. 4486, but it is now commonly known as pempidine (Perolysen May and Baker, or Tenormal I.C.I.).

No detailed pharmacological studies were undertaken in the present series of patients treated with pempidine. Such studies were made by Harrington *et al.*[1] on 32 hypertensives without renal failure and 2 hypertensives with renal failure. They also compared pempidine with mecamylamine. Their findings can be summarized as follows:

1. Like mecamylamine, pempidine is completely absorbed from the gastro-intestinal tract.

2. Both drugs are excreted by the kidneys, and elimination is delayed if there is renal failure.

3. The excretion of both mecamylamine and pempidine is influenced by variation of urinary pH, excretion being reduced by alkalization of the urine, and increased by acidification. However, urinary pH changes affect the excretion of pempidine to a lesser extent than mecamylamine, and pempidine is excreted more rapidly than mecamylamine no matter whether the urine is acid, alkaline or normal.

4. The distribution of both drugs in blood and tissues is much the same, but there is less tissue affinity for pempidine and, unlike mecamylamine, it is not significantly bound to plasma protein. This partly explains the more rapid excretion of pempidine, since a greater fraction of any given dose remains within the extracellular space, and is therefore available for excretion.

5. The minimum lethal dose of pempidine is considerably higher than that of mecamylamine.

6. Both drugs readily cross the blood-brain barrier, and are found in relatively high concentrations in the central nervous system. The pharmacological effects of lethal doses of pempidine in rats are similar to those described for mecamylamine,[2] and include tremor and convulsions.

Clinical Material

Ten patients were treated with pempidine, and the trial extended over a period of about 6 months, but only half of the patients reached the stage of receiving maintenance treatment with pempidine. These patients all had serious hypertension with secondary cardiovascular and retinal changes due to the hypertensive state. Patients were first seen and assessed at the hypertension clinic, and then admitted for further investigations and treatment. Investigations were as thorough and detailed as possible in order to exclude any aetiological condition which might be curable. In none of the 10 cases did we find such an underlying cause.

Of the 10 patients, 5 had malignant hypertension with papilloedema, of which 3 were cases of essential hypertension, 1 chronic nephritis, and 1 a unilateral pyelonephritic kidney. Nephrectomy was performed in the last-mentioned case in an attempt to cure the hypertension, but the hypertension persisted after the operation and a grade-4 retinopathy remained unchanged. The other 5 patients had severe essential hypertension.

There were 6 females and 4 males in the series; 6 were in the relatively young age-group of 30-45 years, while the patient with chronic nephritis and malignant hypertension was a child of 14 years. This child was the only case with a raised blood urea (60 mg. %) at the time treatment was started.

Two patients were in mild hypertensive cardiac failure, and only 2 had previously been treated for hypertension—both with mecamylamine, with an unsatisfactory result.

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† Supplies kindly made available by Imperial Chemical Industries S.A. (Pharmaceuticals) Ltd.

During the initial period in hospital, while investigations were proceeding, all the patients were either sitting up in bed or in a chair alongside the bed, but no other activity was allowed at this stage. To allow for uniformity in the assessment of the drug, salt restriction was not enforced and a normal ward diet was allowed.

Once drug treatment had been started, the patient was encouraged to be up most of the day, and many helped the nurses in some of their minor ward duties. At night they slept in a semi-upright position. These measures allowed for the maximum benefit to be derived from the postural hypotensive effect common to all ganglion-blocking drugs.[5]

CLINICAL TRIAL OF PEMPIDINE

Oral Dosage

Single oral doses of 15 mg. of pempidine bitartrate (7·5 mg. of pempidine base) were given to 5 patients. A similar oral dose of mecamylamine was given to the other 5 hypertensive patients in order to compare the onset duration of action of the two drugs (Fig. 1).

After an oral dose of pempidine a hypotensive effect was usually observed within 1 hour, although in one patient the onset of action was delayed for 3 hours. The total duration of hypotensive action was 6-8 hours. The maximal effect was observed 3-5 hours after the dose, and at this stage most patients developed postural giddiness on standing up from a semi-recumbent position. The additional fall of blood pressure demonstrates the well-known postural hypotension which occurs after the administration of a ganglion-blocking

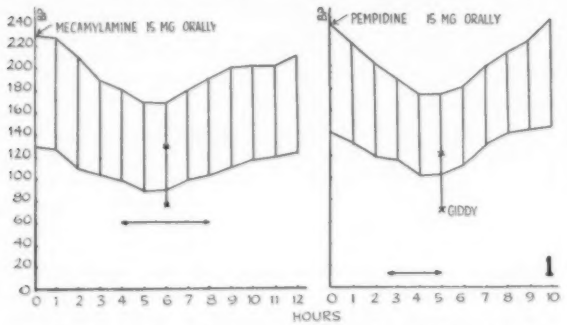

Fig. 1. Comparison of mecamylamine and pempidine given in similar oral doses in respect of onset and duration of action. Arrows indicate duration of postural hypotension and the additional fall of blood pressure on standing is also shown.

drug. The action of pempidine appears to be indistinguishable in this respect from that of mecamylamine and the other methonium compounds used in the treatment of hypertension. The relationship between the extent of the fall of blood pressure in the horizontal posture and the additional fall of blood pressure which occurs on standing varies from patient to patient. Some patients have a substantial fall of blood pressure in all postures with comparatively little postural hypotension. Others have very little fall in pressure when lying flat, but a considerable decrease in blood pressure on assumption of the erect posture.

After an oral dose of mecamylamine, a hypotensive effect was observed after about 2 hours. The total duration of hypotensive action was about 12 hours with the dosage used, although the maximal effect only lasted for 4-8 hours.

Comparing these two ganglion-blocking drugs, it can be seen that similar doses produced a similar hypotensive effect, but that the onset and duration of action is different. Pempidine acts within 1 hour but action only lasts for 6 hours, whereas mecamylamine acts within 2 hours and remains effective for 12 hours. Thus pempidine should be administered 4 times a day, while mecamylamine is usually administered twice a day, though sometimes a smaller or equal midday dose is necessary for optimum control of blood pressure.

With both drugs the resulting fall in blood pressure after a single oral dose was smooth and no undue fluctuation in pressure occurred.

After a single oral dose of 15 mg. one of the pempidine patients developed a severe reaction 6 hours after administration, viz. an acute gastro-intestinal upset with vomiting and diarrhoea, and a few hours later was noted to have some abdominal distension. Such an incident did not occur with any of the mecamylamine patients receiving a single large oral dose. This might suggest that pempidine is the more toxic of the two drugs when both drugs are employed at the same dosage.

Effect of Alteration in Urinary pH on Excretion of Pempidine

It has already been mentioned that Harrington *et al.*[1] showed that the renal clearance of both mecamylamine and pempidine is dependant upon urinary pH, the clearance being increased in an acid urine and decreased in an alkaline urine. Variation in excretion, however, was found to be less with pempidine, and it was stated that the hypotensive effect was therefore less likely to be influenced by changes in acid-base balance than with mecamylamine.[1]

A patient was first given 15 mg. of pempidine orally and showed the expected response as regards the onset and duration of action of pempidine. The patient was then given 12 g. of sodium bicarbonate daily for 2 days, which caused the urine to become alkaline. Another dose of pempidine was then given orally, and showed that a significant increase in the therapeutic action and side-effects of pempidine occurs when the urine is made alkaline. The duration of

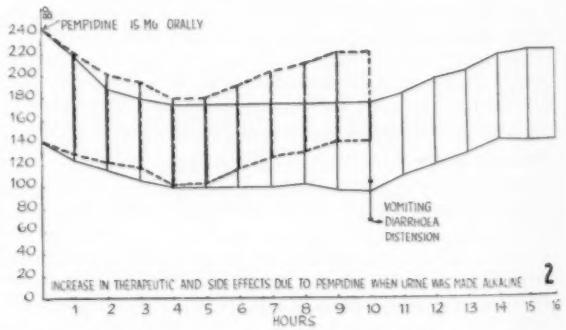

Fig. 2. Increase in therapeutic action and side-effects of pempidine when urine was made alkaline. The curve now resembles the onset and duration curve of mecamylamine. The dotted-line curve shows response to pempidine in the same patient before sodium bicarbonate was given to alkalize the urine.

action was now in the vicinity of 14 hours, and postural hypotension, vomiting and diarrhoea occurred 10 hours after administration. The curve (Fig. 2) closely resembles

the onset-duration curve of mecamylamine, which agrees with the findings of previous workers,[1] who compared the cumulative excretion of pempidine and mecamylamine over 24 hours, while varying the urinary pH. It was found that the lowest rate of excretion of pempidine in an alkaline urine was similar to the highest rate of excretion of mecamylamine in an acid urine.

Acidification of the urine by giving the patient ammonium chloride did not produce a striking alteration in the pempidine onset-duration curve. There was, however, a tendency to a diminished therapeutic effect from the drug, and this one would expect to find due to the more rapid excretion in an acid urine.

Continuous Oral Treatment

Only 10 patients have been observed on continuous treatment with pempidine. They were an unselected group, all of whom had serious hypertension as assessed from symptoms, blood pressure readings, retinal vessels, chest X-ray and electrocardiography. Pempidine was given 4 times during the day, the doses being spaced at 5-hourly intervals from 7 a.m. to 10 p.m. On this regime a sustained reduction in blood pressure may be obtained throughout the day. In some cases the last dose at night was doubled in order to give a prolonged action during the night hours. In one patient with impaired renal function the drug was only given 3 times a day.

Duration of Treatment

Of the 10 patients in the pempidine series, only 5 were eventually discharged from hospital on pempidine, and these were well controlled when they left. In these patients treatment is being continued up to the present time for a period varying from 8 weeks to 20 weeks. Of the remaining 5, one died 3 days after starting pempidine, and treatment had to be stopped in the 4 others because of the severity of side-effects.

Dosage

The dosage of pempidine required to produce an adequate hypotensive effect varied widely, in our series from 10 mg. to 60 mg. daily. The average total daily dose given as maintenance treatment in this series was 40 mg. of the bitartrate. In Harrington's series[1] the corresponding average total daily dose was 32·5 mg.

In our series treatment was usually started with a dose of 2·5 mg. 4 times a day, and raised rapidly by increasing each dose by 2·5 mg. daily until a satisfactory reduction in blood pressure was achieved or the development of toxic effects hampered further progress. Once serious toxic effects occurred, the drug was stopped until the serious symptoms ceased, and then the administration was resumed at a dosage reduced to that previously found to be safe. On this safe dosage, increments were now made with 2·5 mg. of pempidine *per day*. In this way we were able to control at least 3 patients who would have been failures in the trial if the recommended dosage increment of 2·5 mg. *per dose* had been adhered to.[1]

From this experience it appears that the therapeutic and toxic doses of pempidine lie close to each other. We have for instance, found on a few occasions that a dose of say 40 mg. daily produced adequate control of blood pressure, but with severe and limiting side-effects; when the dose was reduced to 37·5 mg. daily, the drug was tolerable yet still therapeutically effective. It is possible that had we tried this dosage scheme earlier on, we might have had more success with pempidine.

Harrington *et al.*[1] did not mention this difficulty in their trial of pempidine. They increased each dose with 2·5 mg. daily until a satisfactory reduction in blood pressure was achieved, and found it possible to reach a stable therapeutic dose level with reasonable safety within a few days.

Tolerance

No evidence has been seen of the development of tolerance to pempidine, analogous to that seen with hexamethonium and other quaternary ammonium compounds.[6] In this respect the drug resembles mecamylamine.

Combination with Other Drugs

In 2 cases reserpine, and in 1 case chlorothiazide, was added to the pempidine. This was done to try and reduce the side-effects of pempidine, and in all 3 cases the combination allowed more successful treatment, suggesting that these compounds potentiate the action of pempidine as has been described with other hypotensive agents.[5]

Side-effects

Side-effects (Table I) occurred with disappointing frequency. Only one of the 10 patients treated with pempidine did not experience troublesome side-effects, and this patient was fortunate enough to have her blood pressure controlled on a very low dosage, viz. 10 mg. per day. Pempidine had to be abandoned in 5 cases because of the severity of side-effects.

TABLE I. SIDE-EFFECTS OF PEMPIDINE (10 PATIENTS)

Alimentary	
Dry mouth	8
Bitter taste	2
Nausea and vomiting	7
Constipation	8
Distention	7
Severe ileus	2
Diarrhoea	3
Urinary	
Difficulty in micturition	2
Retention	1
Visual	
Blurring of vision	3
CNS	
Tremors	2

One of these patients subsequently died, but those remaining have all been successfully controlled with mecamylamine. Of the 5 patients successfully controlled with pempidine, 3 required laxatives regularly to avoid constipation and, of these 3, one also required pilocarpine eye drops for blurred vision, and another neostigmine to relieve the feeling of fullness and distension which accompanied the constipation.

From the list of side-effects (Table I) it will be seen that the most troublesome ones are from the gastro-intestinal tract, and the severity of these were responsible for cessation of therapy in one-half of the patients in this small series. A true ileus with constipation, continuous vomiting and absence of bowel sounds occurred in 2 patients; this must be regarded as a very serious complication.

Retention of urine occurred in one patient, a male of 60 years with malignant hypertension, and pempidine had to be stopped. This patient had previously failed to have his blood pressure controlled on mecamylamine for the same reason. He had a transurethral resection for bladder-neck stenosis, and subsequently we managed to control his blood pressure reasonably well on pempidine.

Our pempidine trial came to an abrupt end when one patient died as a result of a severe ileus, which must be attributed to the drug.

This patient was an African male aged 60 years with severe essential hypertension. He presented with headaches and progressively increasing effort dyspnoea over the previous 2 years. He also had a chronic cough with mucopurulent sputum, and suffered from osteo-arthritis. Blood pressure 250/140 mm. Hg. His heart was enlarged, with a left ventricular type of apex beat, but he was not in cardiac failure. A grade-2 hypertensive retinopathy was found. Routine special investigations did not reveal anything of note. The blood urea was normal.

Penicillin and streptomycin were given for his mucopurulent bronchitis, and syrup of codeine phosphate 6-hourly for the irritating cough. He was started on 2·5 mg. of pempidine 4 times a day on 12 November 1958. Ambulation was encouraged. He was quite well on 13 November, but had no bowel action that day. His blood pressure, taken 4 times a day, averaged 220/120. Agarol was prescribed for constipation, and the next morning, 14 November, 2 days after starting pempidine, he complained of abdominal distension as well as constipation; his abdomen was found to be distended, but bowel sounds could be heard. The blood pressure was then 200/120. His urine was strongly acid. The pempidine was stopped, and the patient was given carbachol, 0·5 mg. intramuscularly. That same afternoon he started vomiting. Abdominal distension had increased, and no bowel sounds could be heard. The blood pressure was now 170/100. The urinary output was satisfactory and the urine was still acid.

Intravenous drip and gastric suction were now started, and the patient was catheterized and continuous bladder drainage instituted. At first he seemed to improve, but during that night he developed severe diarrhoea. When seen on 15 November he appeared to be in a shocked state; pulse 120 p.m., blood pressure 140/100, cold and sweating. The urinary output was 1 litre and the gastric suction 1½ litres during the previous 24 hours. The serum electrolytes estimated at this stage were normal, except for a rather low serum-potassium (3·5 mEq. per litre), despite which the electrocardiogram, except for a tachycardia, was not significantly different from that taken on admission.

The patient received 1½ litres of Darrow's solution, 1 litre of sodium chloride and 2 litres of dextrose water, plus 2 g. of potassium chloride, over the next 24 hours. His condition did not improve, and finally solucortef was also given intravenously *via* the drip.

The blood pressure never fell below 140/100 and urinary output remained satisfactory throughout this period. The patient died later that night (15 November).

At autopsy the pathological diagnosis was paralytic ileus with meteorism, dilatation and early peritonitis of the small intestine. Purulent bronchitis and bronchopneumonia were present in both lungs, the heart showed left ventricular hypertrophy and the kidneys slight nephrosclerosis. An unexpected finding was the presence of numerous amoebic ulcers in the caecum, ascending colon and transverse colon. The patient had never mentioned to us any complaint referable to this.

As a result of this tragic death it was decided to end the clinical trial of pempidine, and we have, temporarily at least, abandoned further use of the drug in the treatment of hypertension. It was interesting to find a recent report[7] of a patient who died of severe diarrhoea after mecamylamine treatment. At necropsy gross ulceration of the colon was present, and this was thought to be due to a direct local effect of the drug. In our patient, however, the treatment was not the cause of the ulcers, for amoebae were seen microscopically.

Results in Cases treated with Pempidine

In 5 patients we obtained a satisfactory control of blood pressure with pempidine as the major drug used in treatment (Table II). Parallel with a fall in blood pressure, there was a general improvement in these patients. Headaches due to hypertensive treatment disappeared and the patient with cardiac failure developed a better exercise tolerance and could dispense with the digitalis and diuretics which he required before this treatment. Of these 5 patients 3 were cases of malignant hypertension, which was successfully treated with pempidine. In all 3, papilloedema disappeared after an average treatment period of 6 weeks.

TABLE II. RESULTS IN 5 PEMPIDINE-TREATED CASES

Average BP (mm. Hg)		*Retina*	*Dose*	
Before	*After*	*(Keith-Wagener)*	*(mg. per day)*	*Side-effects*
260/170	200/120	IV→III	30	Dry mouth Constipation Vomiting Blurred vision.
240/140	160/105	II→II	20	Constipation Dry mouth Bitter taste.
230/130	170/110	II→II	10	—
260/150	180/120	IV→II	60	Severe visual disturbances.
280/160	180/100	IV→II	37·5	Dry mouth Constipation.

Side-effects were troublesome in 3 of the 5 patients and they required additional specific treatment for constipation, dry mouth, blurred vision and a feeling of abdominal distension.

DISCUSSION

Harrington *et al.*[1] also report a syndrome of early paralytic ileus, with vomiting, abdominal pain and distension in 3 out of 27 patients treated with pempidine. In their cases the symptoms cleared completely within 12 hours of stopping the drug. We were less fortunate with this one patient who died, although our other patient who developed ileus recovered fairly rapidly, but even here intravenous therapy and gastric suction were necessary. The only side-effects occuring frequently in Harrington's series of 27 patients,[1] were constipation (66%), dryness of the mouth (66%) and blurring of vision (45%). The complaints were regarded as major in only 3 cases.

In our experience toxic symptoms with pempidine occur early, usually on the same day as the toxic dose is instituted, but in 2 cases side-effects were delayed for 2 days. Parallel with this, a fall of blood pressure has always occurred and in most cases to a satisfactory level from a therapeutic point of view. If the same dosage that produced toxicity originally was given again 1 month later, the same side-effects occurred, showing that no significant tolerance to pempidine developed.

We have also found that there was only a narrow margin between the toxic and therapeutic doses of pempidine. Patients fairly comfortably stabilized on a certain dosage, regularly developed more serious toxic symptoms, such as distension and vomiting, on a dosage increment of as little as 2·5 mg. per day.

Comparison with Mecamylamine

Harrington *et al.*[1] concluded from their study of pempidine that there was little to choose between this drug and mecamylamine in respect of their side-effects. We have, however, been far less successful with pempidine than with mecamylamine. Our 4 pempidine failures were all controlled and discharged on mecamylamine. We had the opportunity of trying only 2 mecamylamine failures on pempidine, and it was unsuccessful and had to be abandoned in both.

If we compare our last 20 patients treated on mecamylamine, we find that control was easier and there were

less interruptions caused by stopping and starting the drug. Consequently the average stay in hospital was shorter.

Side-effects also occurred with mecamylamine, but they were less frequent and less serious. Constipation and dry mouth occurred in less than half of our mecamylamine patients, but in 8 out of 10 of the pempidine series. A true ileus occurred in 2 of our pempidine patients, but in none of the 20 mecamylamine-treated group, although it is a recognized danger with mecamylamine.

SUMMARY AND CONCLUSIONS

Pempidine has been used as a hypotensive agent in 10 patients with severe hypertension. Though the series is small, we have been able to form certain impressions about the drug. Pempidine given by mouth undoubtedly lowers the blood pressure in most patients, by virtue of its ganglion-blocking effect, but it would be wrong to assume that it is an ideal drug for the treatment of hypertension.

Pempidine has many points of similarity to mecamylamine. Both are freely absorbed from the gut, as a result of which a constant therapeutic effect from day to day can be obtained with oral administration. Both are excreted more rapidly in an acid than in an alkaline urine, and both easily cross the blood-brain barrier.[1]

Pharmacologically pempidine has certain advantages over mecamylamine which should make it a potentially more useful drug. It is more rapidly excreted, chiefly because of a lower tissue affinity for the drug, and excretion of pempidine is less affected by variation in acid balance than that of mecamylamine. These pharmacological advantages we have found of relatively little account in practice, and severe side-effects, the main drawback with all ganglion-blocking agents, occur with disappointing frequency. We have found them to occur rather more frequently with pempidine than with mecamylamine, and certainly the gastro-intestinal side-effects from pempidine seem to be more serious.

After losing one patient from a pempidine ileus, we have abandoned further use of the drug in the treatment of hypertension. At the moment we do not feel that it can replace mecamylamine or pentolinium as probably the most useful drugs for the long-term treatment of severe hypertension.

Pempidine might well be held in reserve. Good control over blood pressure can be obtained with it in those patients who are fortunate enough to be able to tolerate it, and since responses to ganglion-blocking drugs are highly individual, it is likely that some patients may be more comfortable on the one drug than the other, whether this be mecamylamine, pentolinium, chlorisondamine or pempidine.

I wish to thank the Medical Superintendent of the Karl Bremer Hospital, Dr. R. L. M. Kotze, for permission to publish this report, and Prof. A. J. Brink for his stimulating advice and criticism and for reading the manuscript.

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A PRELIMINARY STATISTICAL SURVEY OF CARCINOMA OF THE OESOPHAGUS IN THE AFRICAN WITH SPECIAL REFERENCE TO ACQUIRED OESOPHAGEAL FISTULAE

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Fistulae of the oesophagus are frequent among the patients with inoperable oesophageal cancer admitted to the Johannesburg Non-European Hospital over the past 4 years, and hitherto undescribed peculiarities have been noted.

The oesophagus is an organ peculiarly liable to perforation. Even in its normal condition, following closely the course of the lower cervical and thoracic spines, it is comparatively friable. Its situation is far posterior and it is suspended tautly between points of fixation at both upper and lower ends. This naturally diminishes its mobility. It is therefore not surprising that, during attempts to overcome obstruction either instrumental or by natural deglutition, an oesophagus which has a further increase in friability because of disease is not uncommonly subject to fistula. It is with particular reference to this that we feel some conclusions can be drawn.

Oesophageal fistulae may be congenital or acquired. Congenital fistulae have been adequately described in the literature, but the descriptions of acquired oesophageal fistulae have been few and inadequate. The following brief classification of possible causes of acquired fistulae of the oesophagus may be of help in diagnosis:

I. *Neoplastic*. While carcinoma of the oesophagus is the commonest cause of oesophageal fistulae,[1] it is well to remember that fistulae of the oesophagus sometimes occur as a result of extra-oesophageal malignancies of trachea, bronchus, larynx, pyriform fossa,[2,3] and thyroid.[3,4]

II. *Inflammatory*
- (A) *Intra-oesophageal*
  1. *Acute:* Oesophagitis and peptic ulceration.
  2. *Chronic:* (*a*) Tuberculosis,[1,5-7] (*b*) Syphilis.
- (B) *Extra-oesophageal*
  Chronic: (*a*) Tuberculosis of mediastinal lymph glands and empyema, [6-9] (*b*) Actinomycosis.[4,10,11]

III. *Traumatic*[12]
1. Foreign bodies, especially fish and chicken bones.[1,13]
2. Corrosive chemicals—caustic soda, acids, etc.
3. Indirect crush injuries, e.g. 'stove-in' chest.[2]
4. Direct injuries, e.g. gunshot[2] or stab wounds, crush injuries,[1] penetration by fractured bones (ribs, sternum or vertebrae).[2]
5. Instruments (*a*) Dilating bougies, (*b*) Souttar's tube, (*c*) Oesophagoscope.[1]

IV. *Spontaneous rupture*, in cases which have been accounted for by alcohol,[13] severe vomiting,[14] vascular thrombosis and infarctions of oesophageal wall,[2] cardiospasm,[2] oesophagitis and peptic ulceration, strictures,[2] radiation,[13] etc.[1,6,15]

PRESENT SERIES

Referred cases of suspected carcinoma of the oesophagus, after preliminary clinical examination, were investigated radiologically, and accuracy of assessment was increased by endoscopy, biopsy, and examination of stools for occult blood.

Our series of cancer of the oesophagus dates from 1955, since which time we have seen 120 cases, as follows: 15 cases in 1955, 25 cases in 1956, 44 cases in 1957, and 36 cases in 1958. Of these cases 10 were female, i.e. 8·3% or 1 female for every 11 males. This proportional incidence in females is considerably less than that in other surveys, in which the percentage of females varies from 25% to 33%. This difference may well be the result of a greater consumption of carcinogen-containing alcoholic beverages by the African male.[16]

It has been generally accepted that carcinoma of the oesophagus is divisible, according to situation, into 3 main groups—in the upper, middle and lower thirds. We have made these divisions a little more exact by defining them (according to measurements taken from the lower incisor teeth) as being 16-25 cm., 25-35 cm., and over 35 cm. (to the cardiac orifice). Because of inadequate records, details of the exact situation on oesophagoscopy were only available in 50 cases. Of these, 13 cases (26%) presented in the upper third, 32 (64%) in the middle third and 5 (10%) in the lower third. These statistics are at variance with those reported in the literature, as will be seen from the following table, which quotes 2 other series:

	Present Series	*Series A*[17]	*Series B*[18]
Upper third	26%	17%	8%
Middle third	64%	36%	32%
Lower third	10%	47%	60%

The preponderance of carcinoma at the level of the middle third in the present series (as opposed to the lower third in other series) suggests the possibility of a different aetiological factor, which may well, as mentioned above, be a carcinogen-containing drink.

Radiologically, however, our statistics in a series of 29 non-selected consecutive cases showed a slightly different proportion, viz. 77% middle third, 11·5% upper third and 11·5% lower third. We suspect the difference in percentage of levels between those found on oesophagoscopy and those demonstrated radiographically to be due to the fact that the lesion is seen 2-3 cm. higher on oesophagoscopy.

Fistulae

In our study of fistulae, 1957 was taken as a representative year because it was during that year that our interest resulted in fully comprehensive investigations and records. That year the abovementioned 29 cases were radiologically investigated. Of these, 13 presented with fistulae of one sort or another (about 45%). This is a very much higher percentage than in other reported series, and may be due to the more advanced stage at which we see the patients.

Direction of fistulae. In the literature the following directions of fistulae have been described:

1. *Respiratory Tract*
   (*a*) Trachea[1,10,19]
   (*b*) Bronchial tree[1,4,10,19,20]
   (*c*) Lungs[13,19,20]
   (*d*) Pleural cavity[1,6,8,9,13,20-22]
2. *Pericardium*[1,2]
3. *Skin*[1]
   (*a*) Neck[2]
   (*b*) Chest[21]
4. *Mediastinum*[1,13]
5. *Great Vessels*[19]
   (*a*) Subclavian (perhaps aberrant subclavian) artery.
   (*b*) Aorta.
   (*c*) Carotid artery.

In our series we did not encounter all the above, but found the direction of the fistulae to be as follows: 6 cases (46% of the fistulae) into the mediastinum; 5 cases (38%) into the respiratory tree—trachea or bronchi; and 2 cases (15%) into a pleural cavity.

All but 3 of these fistulae were caused by the growth. In trying to correlate the direction of the fistula with the level of the carcinoma we found that in the 6 mediastinal fistulae there was a marked variation of the level of the carcinoma, ranging from the 4th to the 8th thoracic vertebra. In the bronchial fistulae, however, the level of the carcinoma was at the 7th thoracic vertebra in all 5 cases, the maximum deviation being from the lower part of the 6th to the upper part of the 8th thoracic vertebra. In both of the pleural fistulae the level of the carcinoma was at the 10th thoracic vertebra.

Of the 3 fistulae which were not spontaneous but resulted from operative interference, 2 were oesophago-pleural and one post-cricoid. A fistula of special interest was one which presented originally as a spontaneous (carcinogenic) oesophago-mediastinal fistula, and became oesophago-mediastino-bronchial after oesophagoscopy (Fig. 1).

CASE REPORTS

The following are representative fistulae of the various types:

Case 1 (Fig. 2)

A middle-aged African male was to be treated for an inoperable carcinoma of the middle third of his oesophagus with a Souttar's tube containing radium, and 24 hours after the tube had been installed a perfectly comfortable patient was sent for a routine post-operative X-ray of the chest. A hydropneumothorax was seen and an immediate diagnosis was made of oesophago-pleural fistula. This was outlined by means of an iodized-oil swallow and confirmed when, on aspiration of the pleural cavity with a wide-bore needle, lipiodol made its exit together with liquid and semi-solid material which he had imbibed without authority.

[There have been only 2 reports in the literature of oesophago-pleural fistulae caused by carcinoma of the oesophagus and, as far as we know, this is the first occasion on which an oesophago-pleural fistula of carcinogenic origin has been demonstrated with iodized oil. This fact is corroborated by Neuhof and Rabin, who state: 'Although we have not had occasion to make the observation (outlining of oesophago-pleural fistulae with contrast medium) in any of the cases of our series, it is conceivable that the ingested iodized oil may enter the pleural cavity in such an instance.']

Case 2 (Fig. 3)

A middle-aged African male was given a barium swallow for dysphagia. It was noted at fluoroscopy that the right lower-lobe bronchus was outlined *via* an oesophago-bronchial fistula. The trachea and bronchi to other lobes were also seen to contain radio-opaque contrast medium. The latter structures were outlined by inhalation of contrast medium which overflowed in a retrograde direction into trachea from the obstructed oesophagus.

Case 3 (Fig. 4)

A male African was X-rayed (as in case 1) as a routine measuae after a Souttar's tube had been installed for inoperable carcinom

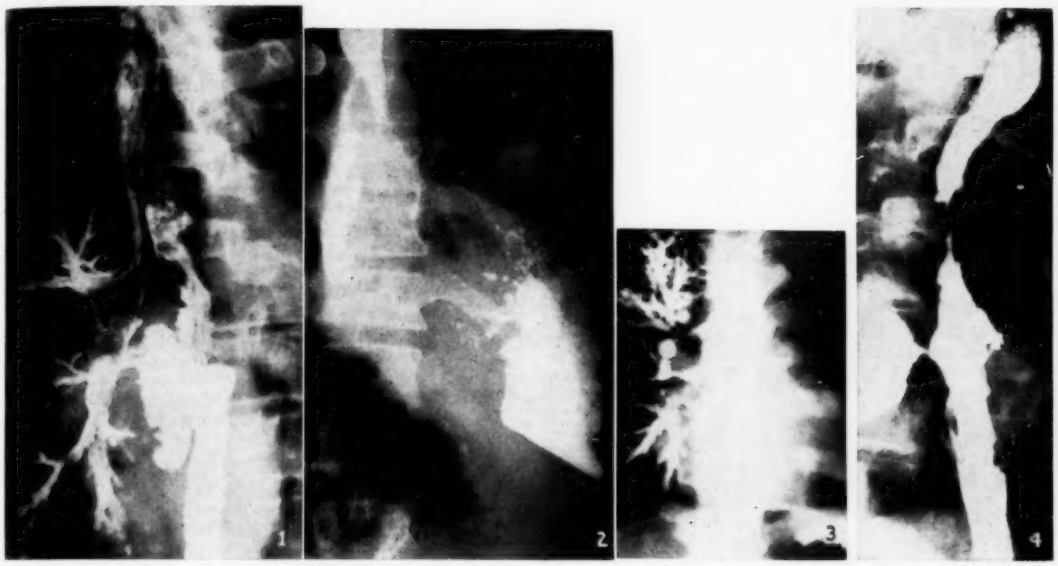

Fig. 1. Oesophago-mediastino-bronchial fistula.
Fig. 2. Case 1. Oesophago-pleural fistula.
Fig. 3. Case 2. Oesophago-bronchial fistula.
Fig. 4. Case 3. Oesophago-mediastinal fistula.

of the oesophagus. It was noted that surgical emphysema was present on the right side of the neck and in the left shoulder region. A diagnosis was made of oesophago-mediastinal fistula and an iodized-oil swallow was given. The fistula was noted to pass from the oesophagus anteriorly and to the right into the mediastinum. This indicates the importance of cervical emphysema as a diagnostic criterion in mediastinal fistulae.

It was noteworthy that only one of our patients with fistulae presented with the severe fulminating symptoms that other authors noted in similar cases. The expected clinical evidence of gangrenous pneumonitis and mediastinitis was also not present.

SUMMARY

1. A series of 120 consecutive inoperable carcinomata of the oesophagus in the African is analysed.

2. The low incidence of cancer of the oesophagus in females is discussed, and a possible reason for it is suggested.

3. In 50 cases examined by oesophagoscopy and 29 by X-ray, the preponderance of growth in the middle third of the oesophagus is stressed.

4. Fluoroscopy and oesophagoscopy levels of neoplastic changes are compared.

5. The high percentage of spontaneous fistulae is noted.

6. Representative case reports are given.

7. In fistulae of carcinogenic origin the absence of fulminating symptoms and of clinical evidence of gangrenous mediastinitis is noted.

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CARCINOSARCOMA OF THE OESOPHAGUS

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Carcinosarcoma of the oesophagus is a rare condition, for there appear to be but 30 cases recorded in the literature.

In 1949 Stout, Humphreys and Rottenberg[1] reviewed 20 reported cases when reporting their own. Six years later King and Koerner[2] added a case and referred to 6 further cases, published in the interim. Since then Poppens, Nicolas and Szanto's case[3] is the only one listed.[9]

Sarcoma of any type is a rarity in the oesophagus for, in the course of making 12,000 barium-meal examinations in White and non-White patients, this is the first case I have

encountered, while carcinoma of the oesophagus is relatively common in non-Whites in South Africa.

CASE REPORT

A Coloured farm labourer aged 45 years, from a fruit district in the Western Cape Province, was referred to the Karl Bremer Hospital, Bellville, early in June 1958 for investigation of difficulty with swallowing and a sensation of obstruction in the oesophagus in the middle of the chest of *one month's duration*. Regurgitation of food was experienced for the same period, during which time the difficulty in swallowing solids became worse and semi-fluid food only could be taken sparingly, with consequent rapid loss of weight. A cough and hoarseness were troublesome.

Examination

The patient was emaciated. No anaemia, jaundice or cyanosis was noted. The cardiovascular, genito-urinary and central nervous systems revealed no abnormality.

Respiratory system. A laryngo-tracheo-bronchitis was present. X-ray changes were apparent in both lung fields, mainly in the mid-zones and bases, suggestive of a spill-and-aspiration phenomenon with increased broncho-vascular striation, as is commonly seen with obstructive oesophageal lesions. An oval soft-tissue mass in the long axis of the mediastinum was visible posterior to the tracheal bifurcation, with a fluid level in a dilated upper third of the oesophagus on a level with the aortic arch.

Barium Meal

There was a high-grade obstruction in the upper third of the oesophagus. The upper edge was at the level of the aortic arch, anterior to D5. An oval mass extended downwards for 9 cm. from here and expanded the lumen of the oesophagus to a width of 6 cm. The oesophagus above the mass was dilated to about twice the average normal diameter. A cupola effect at the upper and lower margins of the mass was seen in the erect and Trendelenburg positions. The barium trickled slowly past the mass, showing a coarse net-like thin layer of barium smeared on its surface but no mucosal pattern. (See Figs. 1 and 2.) The rest of the upper alimentary tract was normal. The appearance was unlike a carcinoma and suggested a benign lesion such as a leiomyoma but the fairly rapid development of symptoms favoured sarcomatous change.

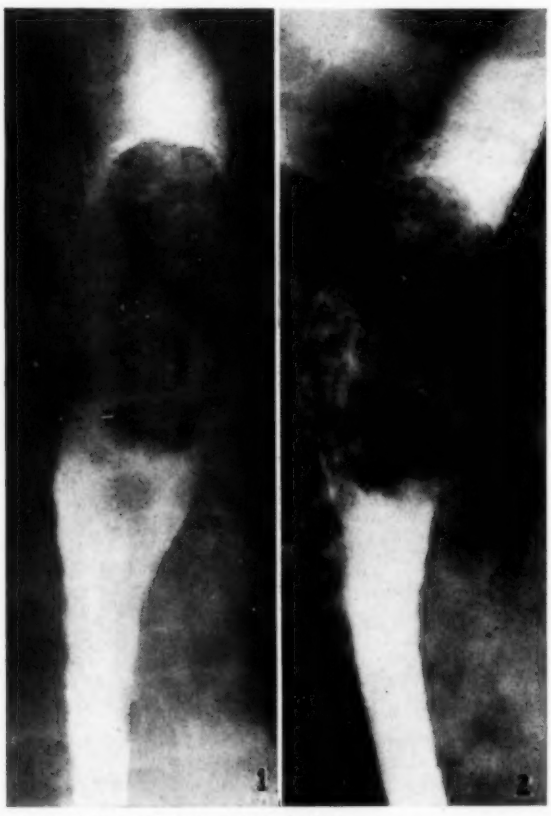

Fig. 1. Barium meal, postero-anterior position.
Fig. 2. Barium meal, oblique position.

Biopsy was performed on 7 June 1958 and the following report from the Department of Histo-pathology (Prof. H. W. Weber) was furnished: 'The specimen consists of 4 small pieces of greyish tissue. The histology is that of a malignant anaplastic tumour consisting of spindle-shaped and round cells with many mitoses. I cannot decide with confidence whether it is a sarcoma or a carcinoma but a spindle-celled sarcoma seems to be more probable.'

Operation

At operation, on 17 June, there was no sign of malignant spread to the mediastinum. The tumour was resected with the lower two-thirds of the oesophagus. The stomach was mobilized and anastomosed to the upper third of the oesophagus, and a pyloroplasty was carried out.

Post-operatively the patient progressed favourably for 5 days and then developed fever, delirium and pulmonary changes. The anastomosis showed no abnormality or leak on radiological investigation. The patient's condition deteriorated and he died on the 12th post-operative day.

The pathological report (20 June) on the specimen stated that there was a large greyish tumour 10 cm. in diameter, which appeared to be a carcinosarcoma consisting of a squamous-cell carcinoma and a spindle-cell sarcoma filling the oesophagus.

Comment

Of special interest was the X-ray appearance in this case, which suggested the intramural, extramucosal origin of the tumour by 4 features,[8] viz. (*a*) the cupola effect with sharply defined margins above and below, (*b*) distension of the oesophagus with absence of mucosal pattern, (*c*) smear effect resulting in a web-like pattern as barium passed over the tumour mass, and (*d*) constancy of shape on respiration unlike a cystic tumour.

The short duration of the symptoms indicated a malignant process but the absence of ulceration and irregularity of contour were quite unlike a carcinoma.

DISCUSSION

The illustrations of reported cases reveal that it is impossible to make the diagnosis on the X-ray signs alone, and that myomata[5-7] and other sarcoma types, e.g. melanosarcoma,[4] and leiomyosarcoma may all present as extramucosal lesions,[8] exhibiting sharply defined rounded defects, some with ulceration. With a short clinical history the diagnosis of sarcoma is a reasonable certainty, for it is very unlike carcinoma.

OPSOMMING

'n Geval van karsino-sarkoom van die slukderm by 'n nie-Blanke pasiënt word beskryf. Die röntgenologiese kenmerke met 'n barium sluk is 'n skerp begrensde tumor wat die slukderm uitsit met koepel fatsoen bo en onder, 'n smeer-effek en spinnerak patroon waar die barium daaroor loop, sonder enige slymvliespatroon of ulserasie en 'n kort geskiedenis van slukbesware wat spoedig toeneem.

Thanks are expressed to Dr. R. Kotze, Medical Superintendent, Karl Bremer Hospital, the Department of Medicine (Prof. A. J. Brink), the Department of Surgery (Prof. F. du T. van Zyl), the Department of Histo-pathology (Prof. H. W. Weber), and the Surgeon, Mr. J. J. W. van Zyl—all of the University of Stellenbosch—who were concerned with the hospitalization and investigation of this case.

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THE SIGNIFICANCE OF THE BACTERAEMIA OF KWASHIORKOR*

P. M. SMYTHE, M.B., M.R.C.P. and J. A. H. CAMPBELL, M.B., M.MED. (PATH.)

From the Departments of Child Health and Pathology, University of Cape Town and Groote Schuur Hospital, Observatory, Cape

As part of a series of investigations into the causes of death in children with kwashiorkor, blood cultures have been carried out both on admission and *post mortem*, the latter always within an hour of death. The results are as follows:

Of a total of 105 cases, 27 had no blood culture (2 of these died), and 78 had blood cultures carried out (25 died, and 53 survived). Of the 53 who survived, 44 had negative blood cultures on admission, and 9 were positive (5 contaminants, 3 coagulase-positive *Staphylococcus aureus*, and 1 blood culture from which was grown both a salmonella and *Diplococcus pneumoniae*).

Of the 25 who died, 9 had negative blood cultures on admission (5 of these were also negative on post-mortem examination, and 4 had no post-mortem blood culture); and 16 had positive blood cultures. Eleven of the 16 were positive on admission (4 *Salmonella typhimurium*, 1 *Salmonella typhimurium* and *Diplococcus pneumoniae*, 2 paracolon, 1 coliform, 2 *Staphylococcus aureus* and 1 *Diplococcus pneumoniae*); and 5 were positive on post-mortem examination (1 enterococcus, 1 l-f coliform, 1 *Pseudomonas aeruginosa*, 1 paracolon, and 1 monilia). Three of these had negative blood cultures on admission and in 2 no blood culture was carried out on admission.

In considering the implications of the positive blood cultures obtained on admission, it is difficult to escape the conclusion that this is a significant finding since 11 out of 15 of these children died. The frequency with which *Salmonella typhimurium* was cultured also deserves comment as it is out of proportion to the general incidence of this organism found on stool culture.

The interpretation of the positive post-mortem cultures is much more difficult. In an endeavour to evaluate their significance a control series of post-mortem blood cultures have also been carried out on children dying from other causes. So far in 6 cases of gastro-enteritis only one positive blood culture has been obtained.

Post-mortem material from these children dying with kwashiorkor has also been examined for any alternative cause of death. Out of 16 cases 7 showed an adequate cause of death, 5 had lesions that were thought to be inadequate as a cause of death and in 4 no lesions were found. Although no definite conclusions can be drawn from the post-mortem blood cultures, since a satisfactory cause of death was found in less than half of the cases at autopsy, it seems reasonable to consider the implications of the positive blood cultures at least until a satisfactory alternative cause of death is found.

The frequency with which intestinal bacteria were found would suggest that there has been a break in the intestinal barrier that limits bacterial invasion. It also suggests a disturbance of the normal immune mechanism that destroys any intestinal bacteria that gain entrance to the blood stream.

Histological examination of the intestine in 9 cases of kwashiorkor showed ulceration of the mucous membrane in one. A striking finding in 2 cases was small mucous inclusion cysts similar to those described by Denton[1] in adults dying of pellagra and not previously described in kwashiorkor. Both these changes might predispose to the entry of excessive numbers of bacteria into the blood stream. Even though in most cases the mucosa appeared intact, this does not exclude the entry of bacteria into the blood stream[2] where they should be destroyed by the immune mechanism of the body.

The immunity state of children with kwashiorkor is generally held to be fairly good. Children are nursed in the general childrens' ward without being particularly prone to infection. If infection is present they respond fairly well to treatment. Their gamma-globulin levels are usually raised or normal. Immunity in kwashiorkor seems to have been largely correlated with gamma-globulin levels, but the pattern of infection is unlike that of children with agammaglobulinaemia. Meningitis is rare, severe staphylococcal skin infections are uncommon and, although pneumonia occurs frequently, response to treatment is fairly good. Furthermore, Janeway and Gitlin[3] have commented on the rarity of infection due to intestinal bacteria in children with agammaglobulinaemia and have suggested that this is due to their having a normal properdin mechanism.

Properdin is a euglobulin first described by Pillemer.[4] It has been shown to be bactericidal to shigellae, strains of salmonella, paracolobacterum, pseudomonas, proteus, escherichia and bacillus. A defect in properdin production in kwashiorkor could well explain the high incidence of intestinal bacteria found on blood culture.

There is a close similarity in the response to infection of children with kwashiorkor to that seen in premature infants and neonates. Signs of inflammation are often lacking with no fever or leucocytosis. (None of these children with positive blood cultures on admission showed clinical signs of septicaemia.) Lesions are often gangrenous rather than pyogenic. Sudden death is quite common, and there is a greater frequency of infections with Gram-negative organisms of intestinal type. Of particular interest is the finding by McKenzie, Hansen and Becker[5] of generalized herpes simplex in a number of fatal cases of kwashiorkor as nearly all previous cases have been in the neonatal age group. This also suggests a common defect in the immune mechanism which may well be properdin.

Should a properdin deficiency be found in some cases of kwashiorkor and neonates it may play a part in the sudden deaths to which both states are prone. Fine[6] has shown experimentally that the state of irreversible shock is associated with an invasion of the tissues by intestinal bacteria, and Frank *et al.*[7] have demonstrated that there is a coincidental fall in properdin blood levels.

Further investigations are required into the exact significance of these positive blood cultures in children with kwashiorkor. Meanwhile the positive blood cultures seem to supply an additional reason for the routine use of powerful antibiotics in the treatment of the disease.[8] No delay in awaiting laboratory confirmation of the diagnosis is justified, since, with one exception, all deaths in this series occurred within 5 days of admission to hospital.

We wish to thank Prof. A. Kipps of the Department of Bacteriology, University of Cape Town, for the blood-culture examinations and for his help and advice.

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* Abstract of paper presented at Research Forum, University of Cape Town, 19 May 1959.

UNIVERSITEITSNUUS : UNIVERSITY NEWS

GENEESKUNDE-BIBLIOTEEK VAN DIE UNIVERSITEIT VAN STELLENBOSCH

In die loop van die jaar het die geneeskunde-biblioteek van die Universiteit van Stellenbosch te Bellville sy ou tuiste in die kliniese gebou, agter die Karel Bremer-Hospitaal, verlaat en intrek geneem in die nuwe tydelike gebou wat deur die Kaaplandse Provinsiale Administrasie vir dié doel opgerig is. Die biblioteek bestaan uit 'n leeskamer, wat ook die boekrakke huisves, 3 kantore, 'n donkerkamer, mikrofilm-leeskamer, pakkamer en kleedkamer. Die totale vloeroppervlakte is 18,785 vk. vt.

Geneeskunde-biblioteek

Twee professionele assistente, 'n klerklike assistent en 'n skoonmaker bedien die biblioteek.

Danksy ruime voorsorg vir boeke en tydskrifte van die kant van die Universiteitsowerheid brei die versameling vinnig uit en is daar reeds 'n goeie basis ‚springlewendige' materiaal om op voort te bou. Die geneeskunde-biblioteke van die Universiteite van Kaapstad, Witwatersrand en Natal, en ook mediese praktisyns, het by wyse van skenkings aansienlik bygedra tot die opbou van volledige tydskrifreekse wat 'n waardevolle deel van die versameling uitmaak. Die geneeskunde-biblioteek van die Universiteit van Kaapstad het uit die staanspoor uit onbaatsugtig meegehelp met daaglikse dienste en Stellenbosch is aan dié inrigting baie dank verskuldig.

Die boekery bestaan tans uit ongeveer 6,000 boekdele waarvan meer as 3,000 ingebonde tydskrifte is. Daar word lopend ingeteken op ongeveer 360 tydskrifte. Die biblioteek is ingeskakel by 'n hele aantal buitelandse uitruildienste.

Gesteun deur 'n outeurs- en titelkatalogus word 'n sistematiese onderwerpskatalogus opgebou en die klassifikasie van die boekery geskied volgens die sisteem van die National Library of Medicine van die V.S.A.

Van Januarie 1959 af word daar gereeld 'n maandelikse lys van nuwe aanwinste versprei. Die biblioteek beskik ook oor 'n foto-dupliseerdiens.

Hoewel gehuisves in 'n tydelike ‚opslag'-gebou, is daarin geslaag om die biblioteek gesellig maar waardig in te rig soos reeds deur menige besoeker getuig is.

42ND MEDICAL CONGRESS (M.A.S.A.), EAST LONDON, 27 SEPTEMBER—3 OCTOBER 1959
42STE MEDIESE KONGRES (M.V.S.A.), OOS-LONDEN, 27 SEPTEMBER—3 OKTOBER 1959

TRANSPORT TO CONGRESS

Opening of East London Airport

There is a possibility that the East London Airport will be open by approximately 15 September. If the Airport is open in time for Congress it will, however, only be possible for Dakotas to land until work on the new runways is completed, and the South African Airways will then operate a shuttle service from Port Elizabeth to East London.

It is suggested, therefore, that delegates ascertain whether aircraft will be landing at East London before making final travelling arrangements. If further information is available before Congress opens it will be published in next week's *Journal*.

The Transport Convenor of the Organizing Committee of Congress has announced that an error appeared in the notice published in the *Journal* of 1 August (33, 653) in which it was stated by the Committee that air reservations to Congress should be made only through S.A.R. & H. travel bureaux. It is not necessary for delegates to book through a S.A.R. & H. travel bureau, they are at liberty to make arrangements through their usual travel agent, who will have been fully informed about the alternative arrangements for air travel to East London.

SCIENTIFIC AND TRADES EXHIBITION

Following are details of the products to be featured by some of the pharmaceutical firms participating in the Exhibition at Congress:

Westdene Products (Pty.) Ltd. (Stand No. 26)

Degranol (mannomustin hydrochloride), an antineoplastic and cytostatic preparation which has been shown to have a definite role in the treatment of malignant disease.

Alcos-Anal (Camden), for the treatment of haemorrhoids (as opposed to symptomatic relief). Alcos-Anal causes permanent shrinkage by stimulation of the perivascular tissue. Available as suppositories and ointment.

Parafon (McNeil) combines Paraflex, the effective low-dosage skeletal muscle relaxant, with Tylenol, the preferred analgesic. Parafon relieves pain and stiffness and helps improve function in acute and chronic low back disorders. It is also available with prednisolone for its anti-inflammatory action.

Lenic (Chemway), an unsaturated fatty acid complex for hypercholesterolaemia.

Teflon, a new surgical prosthesis with low tissue reactivity which is resistant to flex abrasion, non-kinking and retains strength with age.

Diagnostic Instruments of Choice—Welch Allyn.

Medical Books. As in the past, there will be available for inspection a representative selection of the latest editions of surgical and medical books.

British Drug Houses (South Africa) (Pty.) Ltd. (Stand No. 22)

Secrosteron, a new fundamental discovery from the research laboratories of British Drug Houses Ltd., London, is a synthetic purely progestational substance, with many advantages over existing forms of treatment. It has been shown to have no androgenic, oestrogenic or anabolic activity and to be approximately 12 times as potent as ethisterone in biological studies. Because of the absence of side-effects with Secrosteron it can be given in higher dosages than other progestational agents and it produces a more uniform response. Secrosteron is issued in 5 mg. tablets and is given according to a simple dosage schedule.

Distaquaine V-K Suspension, a new product which is a ready-prepared suspension of Distaquaine V-K, each teaspoonful containing 125 mg. of potassium penicillin V. Unlike earlier suspensions of this type it needs no preliminaries whatsoever and is ready to take straight from the spoon. The pleasant flavour and consistency of the preparation appeal to patients of all ages and experience to date clearly indicates that Distaquaine V-K

suspension has little tendency to cause gastric upset or other untoward reactions.

Cobadex Ointment, a unique preparation containing 1% of hydrocortisone B.P. in a 20% water-repellent silicone base. Cobadex is of particular value in contact dermatitis. Healing of the inflammatory lesion is accelerated by the hydrocortisone and at the same time the barrier-cream base prevents the perpetuation of the contact with the primary irritant. Cobadex has also been found of value in dry eczema, napkin rash, intertrigo and care of ileostomy and colostomy openings.

Ancoloxin Tablets contain 25 mg. of meclozine hydrochloride and 50 mg. of pyridoxine hydrochloride per tablet. Ancoloxin is primarily indicated in the nausea and vomiting of pregnancy, but it is also indicated in other conditions which are associated with intractable vomiting in which meclozine hydrochloride is given for central control and pyridoxine hydrochloride for basic nutritional restoration.

Ancofen, a new help for the migraine sufferer, which has been formulated to provide relief from the 4 principal groups of migraine symptoms namely, throbbing unilateral headache, nausea and vomiting, sensory aura, and malaise. Ancofen contains ergotamine tartrate, meclozine hydrochloride, and caffeine. It is generally quite free from side-effects, but a relatively small number of patients may become slightly drowsy due to the sedative action of meclozine hydrochloride if a particularly high dosage of Ancofen is given.

B.L. Pharmaceuticals (Pty.) Ltd. (Stand No. 16).

Kantrex, the new antibiotic developed by Bristol Laboratories International, is rapidly becoming the 'first choice' antibiotic for use in soft tissue infections, genito-urinary infections, and respiratory tract infections due to staphylococcal or gram-negative organisms.

Bristab is hydroflumethiazide, a new orally effective non-mercurial diuretic.

Tetrex, the original tetracycline phosphate complex, is available in capsules, syrup, paediatric drops, intramuscular and intravenous forms.

Uropol, a formulation for the treatment of urinary tract infections. It is now available as a syrup as well as capsules.

Kectil, the well-kown product for control of specific and non-specific diarrhoeas.

PASSING EVENTS : IN DIE VERBYGAAN

Dr. J. J. Frick, of Bloemfontein, is at present doing a 2-year residency postgraduate course at the Louise Obici Hospital, Suffolk, Virginia, USA, which is run in conjunction with the Medical College of Virginia, Richmond, Va., USA. Dr. Frick will return to the Union in August 1961.

* * *

Mr. Louis A. du Plessis, thoracic surgeon, has changed his address from Florence Nightingale Building to 302 Ingram's Corner, Twist Street, Hillbrow, Johannesburg. Telephone numbers remain unchanged: Rooms 44-8837, residence 41-4090.

Dr. Louis A. du Plessis, torakschirurg, het sy adres verander van Florence Nightingale-Gebou na Ingram's Corner 302, Twiststraat, Hillbrow, Johannesburg. Telefoonnommers bly onverander: Spreekkamer 44-837, woning 41-4090.

* * *

Mr. M. A. Lautré, F.R.C.S., has returned to Johannesburg after a 3-month's study trip to England and the Continent.

* * *

The South African Society of Occupational Health (*M.A.S.A.*) will hold a film evening on Tuesday 22 September at 8.15 p.m. at Medical House, Esselen Street, Johannesburg. The first film to be shown deals with 'Stress' and illustrates clearly and adequately the adaption syndrome as elaborated by Dr. Hans Selye. The other film is being shown to the medical profession in this country for the first time and deals with 'Alcoholism'. This film was prepared by Professor Hans-Hoff (Vienna), Dr. E. Beresford-Davies (England), Dr. H. Pullar-Strecker (England), Dr. P. Uhry (France), Dr. M. Cirilli (France), and Dr. C. Lundquist (Sweden). These films have been supplied through the courtesy of Messrs. Pfizer International. Prof. L. A. Hurst, Head of the Department of Psychiatry and Mental Health, University of the Witwatersrand, will comment on the films.

[In order to facilitate seating arrangements, will doctors please notify Dr. B. Serebro, the Hon. Secretary of the Society, of their intention to be present (129 Union Centre, 31 Pritchard Street, Johannesburg).]

* * *

Universiteit van Stellenbosch, Hart-long Groep. 'n Maandelikse bespreking sal gehou word by die Karl Bremer-Hospitaal, mediese skool geboue, Bellville, Kaap, op die eerste Donderdag van elke maand om 8 nm. By die eerste vergadering wat gehou is op 3 September, is daar 'n film oor angio-kardiografie vertoon deur dr. B. J. v. R. Dreyer, en een oor 'n kongenitale harttoestand, nl. atrioventricularis communis, voorgedra deur prof. A. J. Brink.

* * *

Dr. L. Potgieter, wat die afgelope 15 maande kardio-vaskulêre navorsingstudies onderneem het aan die Lankenau-Hospitaal, Philadelphia, V.S.A., het onlangs teruggekeer om sy werk te hervat in 'n voltydse hoedanigheid in die Afdeling Interne Geneeskunde, Universiteit van Stellenbosch, by die Karl Bremer-Hospitaal, Bellville, Kaap.

South African Institute for Medical Research, Johannesburg, Staff Scientific Meeting. A meeting will be held at 5.10 p.m. in the Institute Lecture Theatre on Thursday 17 September when Dr. Harold Stewart, Chief Pathologist to the National Institutes of Health, Bethesda, Maryland, USA, and Chairman of the U.I.C.C. Committee on Geographical Pathology, will give a lecture on 'The intensified WHO research programme'. Tea will be served and visitors will be welcome.

* * *

Southern Transvaal Branch (*M.A.S.A.*). Prof. George E. Burch, Professor of Medicine, Tulane University School of Medicine and the Charity Hospital of Louisiana, New Orleans, will address a meeting on Tuesday 22 September at 8 p.m. in the Harveian Lecture Theatre, Medical School, Hospital Street, Johannesburg. The subject of Professor Burch's talk will be 'The mechanical peculiarities of the heart as a pump'. This meeting will be held under the auspices of Johannesburg Sub-group of the Association of Physicians of South Africa (M.A.S.A.) and the Transvaal Cardiac Society.

* * *

University of the Witwatersrand, Medical Graduates Association. The 7th Alumni Dinner of this Association will take place on Wednesday 16 September at the Auto Club, Killarney, Johannesburg. Cocktails commence at 6.30 p.m. This dinner is in honour of the graduates of 1935 and their teachers. The address of welcome will be presented by Dr. A. M. Porter, President of the Association, and the toast to the Alumni will be proposed by Dr. I. J. Balkin and replied to by Prof. H. B. Stein. The toast to the teachers will be proposed by Dr. W. H. Lawrance and answered by Prof. E. H. Cluver. Wives of members attending will be welcome. For table reservations contact the Secretary, Medical Graduates Association, telephone 44-7040 (mornings).

During the evening a presentation to Prof. E. H. Cluver will be made in recognition of his many years of service and on the occasion of his retirement.

* * *

The Somerset Hospital, Cape Town, a direct descendant of the Cape's first hospital founded by Jan van Riebeeck in 1656, celebrated its 100th anniversary on 18 August 1959. Among the guests present at the reception held at the Hospital to mark the occasion were some of the many doctors and nurses who received their training in this Hospital. Dr. L. Blumberg, Chairman of the Somerset Hospital Board, was the host at this reception and the Administrator of the Cape Province, Dr. the Hon. J. H. O. du Plessis, was the guest of honour.

The Hospital Board published a special brochure to celebrate the centenary of the Hospital. This brochure, written by Col. C. Graham Botha, former Chief Archivist for the Union, contains an interesting historical sketch of the development of the Hospital and of medical services in this country during its early days.

Noord-Transvaalse Tak (M.V.S.A.), Pers-skakelbeampte. Op die jongste vergadering van die Takraad is besluit om dr. J. K. Bremer aan te stel as pers-skakelbeampte van die Tak. Hierdie aanstelling is gemaak teneinde die onakkurate, sensasionele en dikwels misleidende mediese berigte wat in die pers verskyn te voorkom. Lede van die Tak word ernstig versoek om self geen onderhoude of inligting aan joernaliste toe te staan nie (met die uitsondering van lede wat uit die aard van hulle amp sulke inligting moet verskaf), maar om alle navrae te verwys na dr. Bremer wat die nodige inligting sal verskaf.

Oorsese spreker. Prof. T. Antoine, van Weenen, Oostenryk, sal Pretoria van 16 tot 19 September besoek. Hy is Hoogleraar in Verloskunde en Vrouesiektes aan die Universiteit van Weenen en is ook President van die Internasionale Federasie van Verloskunde en Vrouesiektes. Professor Antoine sal om 2 nm. op Vrydag 18 September 'n lesing in die Boonste Lesingsaal, Kliniese Gebou, Algemene Hospitaal, lewer. Alle belangstellendes word uitgenooi om die lesing by te woon.

* * *

Northern Transvaal Branch (M.A.S.A.). Prof. R. McWhirter of the Department of Radiotherapy, Royal Infirmary, Edinburgh, will address a meeting of the Branch on Thursday 8 October at 8.15 p.m. in the Upper Lecture Theatre, Clinical Building, Pretoria General Hospital. His subject will be 'The endocrine control of breast cancer'.

* * *

M. D. Gown. The widow of the late Dr. H. S. Roseman, M.D. (Dubl.) is willing to give Dr. Roseman's M.D. gown to anyone wishing to own one. It has been suggested that anyone who acquires the gown might make a donation to the Benevolent Fund of the Association in recognition of Mrs. Roseman's gesture. Further information may be obtained from the Hon. Secretary of the Northern Transvaal Branch (M.A.S.A.), Dr. O. V. S. Kok, at Room 4, Administrative Building, General Hospital, Pretoria (telephone 2-9741, ext. 211).

* * *

Dr. Geoffrey Dean, M.D., M.R.C.P. (Lond.), of Port Elizabeth, has been appointed to a Commission on Geomedical Research of Diseases of the Nervous System by the World Federation of Neurology. It is hoped that this Commission will hold a Conference during the 7th International Neurological Congress in Rome in September 1961.

Dr. L. J. A. Loewenthal, of Johannesburg, has been made an Associate Editor of *Hautarzt* and a Corresponding Member of the Argentine Dermatological Society.

* * *

Northern Areas Division, Cape Western Branch (M.A.S.A.). The monthly meeting of the Division will be held in the Banqueting Hall, Civic Centre, Voortrekker Road, Parow, on Thursday 17 September at 8.15 p.m. (telephones 98-8461/3). Dr. Justin van Selm will speak on 'Eye problems in general practice' and Dr. Braeme Goldman will speak on 'Ear, nose and throat problems in general practice'. All practitioners will be welcome at this meeting.

Afdeling Noordelike Gebiede, Tak Wes-Kaapland (M.V.S.A.). Die maandelikse vergadering van hierdie Afdeling sal in die Banketsaal, Burgersentrum, Voortrekkerweg, Parow, op Donderdag 17 September om 8.15 nm. plaasvind (telefone 98-8461/3). Dr. Justin van Selm sal oor 'Oogmoeilikhede in algemene praktyk' praat en dr. Braeme Goldman sal oor 'Oor-, neus- en keelmoeilikhede in algemene praktyk' praat.

* * *

Southern African Cardiac Society, Cape Province Section. Prof. George E. Burch, Professor of Medicine, Tulane University of Louisiana, New Orleans, USA, will give a lecture on 'Clinical aspects of spatial vectorcardiography' to this Society on Thursday 24 September in the E-floor lecture theatre, Groote Schuur Hospital, Observatory, Cape. This meeting will be held under the combined auspices of the S.A. Cardiac Society, the Association of Physicians of South Africa, Cape Western Group (M.A.S.A.), and the South African Paediatric Association, Cape Town Sub-group (M.A.S.A.). All who are interested are invited to attend this meeting.

* * *

A History of Medicine in South Africa. Mnr. A. A. Balkema, die uitgewer van *A History of Medicine in South Africa,* het die *Tydskrif* versoek om aan lede van die Vereniging mee te deel dat die boek in aflewerings na verskillende gebiede gestuur word. Daar is dus die moontlikheid dat daar 'n vertraging kan wees voordat al die lede hulle eksemplare ontvang het. Enige lid wat graag sy eksemplaar dadelik wil hê, word versoek om te skryf aan Mnr. Balkema, Union House, Koningin Victoriastraat, Kaapstad. Sy bestelling sal dan onmiddellik uitgevoer word.

CORRESPONDENCE : BRIEWERUBRIEK

SOUTHERN TRANSVAAL BRANCH : DONATION TO BENEVOLENT FUND

To the Editor: The Southern Transvaal Branch of the Medical Association has once again risen splendidly to the occasion by making a donation of no less an amount than £2,532 0s. 7d. to the Benevolent Fund of the Association.

This is a great achievement for which our grateful thanks are due to Mrs. Girdwood, wife of the President of the Branch, and the ladies who so willingly assisted her in such a wonderful effort.

On behalf of my Committee it is a great pleasure for me to express our appreciation of this very remarkable contribution to the Benevolent Fund.

Alan W. Sichel
Chairman, Management Committee of the Benevolent Fund

National Mutual Chambers
Church Square
Cape Town
26 August 1959

DOCUMENTATION ON X-RAY REPORTS

To the Editor: One of my present endeavours is to collect documentation on X-ray reports, i.e. those somewhat ephemeral texts in which the roentgenologist lists and interprets the findings elicited during diagnostic (fluoroscopic and/or roentgenographic) examinations.

Since literature on this topic is relatively scarce, bibliographic indications, perhaps reprints, in any language, would be of help. Quotable sentences on what should, or on what should not, be included in X-ray reports, are also invited. Most of all the undersigned would like to receive originals of X-ray reports, in any language, dated prior to 1910, or more recent ones, if signed by renowned radiologists. Incidentally, does anybody know who wrote the first X-ray report?

The original X-ray reports received, after being photographed for possible reproduction, will be returned to the sender, if so desired, or else retained for an exhibit. Needless to emphasize, proper source credit would be forthcoming in the event of publication.

Please mail all communications to:

E. R. N. Grigg, M.D.

Box 293, Champaign
Illinois, USA
25 August 1959